CASE REPORT

Statin-associated rhabdomyolysis triggered by drug–drug interaction with itraconazole

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SUMMARY

A 47-year-old woman had been treated with high-dose simvastatin for several years. After systemic treatment with the antifungal agent itraconazole, she developed muscle pain and highly elevated levels of creatine kinase and myoglobin. Muscle biopsy was compatible with statin-associated rhabdomyolysis, probably caused by a drug–drug interaction between simvastatin and itraconazole. The patient made full recovery. Three commonly used statins—simvastatin, atorvastatin and lovastatin—are metabolised by the liver enzyme CYP3A4. Several potent inhibitors of this enzyme are known, for example, azole antifungal agents such as itraconazole and posaconazole. If antifungal treatment is indicated in a patient using a CYP3A4-metabolised statin, we recommend (1) topical administration of the antifungal agent if possible, (2) the use of a non-CYP3A4-inhibiting antifungal drug such as terbinafine or (3) temporary discontinuation of statin treatment.

BACKGROUND

3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, better known as statins, are widely used in the prevention of atherosclerotic disease and cardiovascular events.¹ Statins are generally well tolerated, with muscle pain as the most common side effect.^{1–2} Rhabdomyolysis (muscular necrosis) is a very rare, but serious complication, that, left untreated, may lead to renal failure and death.² Statin-induced rhabdomyolysis is triggered by very high plasma levels of statins in plasma.² The majority of statins undergo hepatic metabolism through the cytochrome P450 (CYP) system, and inhibition of the CYP system by other medications may therefore result in highly elevated plasma concentrations and ultimately rhabdomyolysis.^{2–4} Pharmacokinetic drug–drug interactions are the most common cause (60% of cases) of statin-induced rhabdomyolysis.² Increased knowledge of the pharmacokinetic traits of statins among physicians handling patients in statin therapy is needed to prevent these complications.

CASE PRESENTATION

A 47-year-old woman was admitted to the emergency department due to muscle pain. She had received simvastatin 80 mg one time per day and metformin 500 mg two times per day for several years due to hypercholesterolaemia and type 2 diabetes. In addition, she was treated with pregabalin 150 mg two times per day due to neuropathic pain. On admission, she presented with generalised tenderness and weakness of the muscles. There had

been no trauma, fever or infection prior to the onset of symptoms, nor had any herbal medications or toxic substances been taken.

The patient had been treated with simvastatin 80 mg one time per day for several years. She had tolerated the treatment well, and the last measured creatine kinase value 1 year prior to admission had been within the normal range (101 units/L, normal range 50–150 units/L). Three weeks before admission, she had presented a red and itchy rash located at the thorax and arms to her general practitioner. She had been prescribed a 10-day course with itraconazole capsules (100 mg one time per day) based on clinical suspicion of a localised dermal fungal infection.

INVESTIGATIONS

On admission, the suspected diagnosis of rhabdomyolysis was confirmed by a highly elevated creatine kinase (30.855 units/L) and myoglobin (5.046 µg/L, normal range <75 µg/L). The renal function was preserved (plasma-creatinine 51 µmol/L, normal range 45–90 µmol/L).

DIFFERENTIAL DIAGNOSIS

A computer tomography of the thorax, abdomen and pelvis and a muscle biopsy showed no signs of malignancy or primary dermatomyositis. Histological examination of the muscle biopsy was compatible with statin-associated myopathy. As itraconazole is a known inhibitor of simvastatin's liver metabolism, it was concluded that the most plausible cause of rhabdomyolysis was high simvastatin plasma concentrations caused by concomitant treatment with high-dose simvastatin and itraconazole.

TREATMENT

Simvastatin was discontinued shortly after admission and the patient received aggressive intravenous fluid therapy with crystalloids at the intensive care unit of the hospital.

OUTCOME AND FOLLOW-UP

Levels of creatine kinase and myoglobin decreased to near-normal levels within few days (day 3: CK 4637 units/L and myoglobin 204 µg/L). The renal function remained unaffected throughout the course. She was discharged to her home on day 6.

One month after discharge, only minor symptoms (primarily muscle weakness) remained, and creatine kinase and myoglobin had normalised. Treatment with simvastatin had not been resumed.

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DISCUSSION

Simvastatin is, like atorvastatin and lovastatin, primarily metabolised by the P450 enzyme CYP3A4; the dominating enzyme in the CYP system.³ The capacity of CYP enzymes can be lowered substantially in the presence of an inhibitor drug, resulting in decreased metabolism and increased plasma concentrations of substrate drugs. The antifungal azole derivatives itraconazole, ketoconazole and posaconazole are very potent and effective inhibitors of CYP3A4.⁴ All have been shown to cause an at least fivefold increase in the plasma concentration of simvastatin in drug–drug interaction studies performed in healthy volunteers,^{3 5 6} and rhabdomyolysis in the context of concomitant use of simvastatin and itraconazole has been described in case reports similar to the present one.^{7–10} The present case contributes by further confirming the clinical relevance of the drug–drug interaction in younger patients, as the prior reported cases have been in elderly patients with several comorbidities and comedications.^{7–10}

A similar effect of itraconazole, ketoconazole and posaconazole on the metabolism of atorvastatin and lovastatin can be expected, although simvastatin is the statin most susceptible to inhibition.^{3 4} Although fluconazole is considered only as a mild to moderate inhibitor of CYP3A4,⁴ there have been reports of rhabdomyolysis when combining fluconazole with simvastatin or atorvastatin.^{11 12} Voriconazole, clotrimazole and miconazole all inhibit CYP3A4, and theoretically inhibit the metabolism of simvastatin, lovastatin and atorvastatin.⁴ However, no clinical examples of such interactions have been described.

Owing to the risk of severe myalgia, including rhabdomyolysis, concomitant treatment with CYP3A4-metabolised statins and potent inhibitors of CYP3A4 are generally contraindicated.^{2 3} Other potent and effective inhibitors of CYP3A4 include erythromycin and clarithromycin, some protease inhibitors (eg, ritonavir and indinavir) and ciclosporin.³

Treatment of fungal infections in statin-treated patients is common in everyday clinical practice. We thus propose a simple and practical algorithm that can be applied when antifungal treatment is needed in a patient treated with simvastatin, atorvastatin or lovastatin:

1. ensure microbiological confirmation before initiation of systemic antifungal treatment,
2. use topically applied treatment (eg, crème) whenever possible,
3. the majority of fungal strains are susceptible to several antifungal agents; choose a non-inhibiting drug (eg, terbinafine) if possible,
4. If use of a CYP3A4 inhibitor cannot be avoided (ie, in the presence of fungal resistance), discontinue statin treatment temporarily from at least 2 days before until 2 days after antifungal treatment.

Switching to another statin with less potential for a specific drug–drug interaction has also been suggested.⁸ We discourage this approach because the majority of antifungal treatments are short-term, and intermittent discontinuation of statins is unlikely to affect long-term cardiovascular prognosis.

Furthermore, we encourage the implementation of systems that can capture serious drug–drug interactions during prescribing and dispensing of drugs.

Learning points

- ▶ A pharmacokinetic drug–drug interaction is the most common cause (60% of cases) of statin-induced rhabdomyolysis.
- ▶ Simvastatin, atorvastatin and lovastatin are metabolised by the P450 enzyme CYP3A4 which makes them susceptible to drug–drug interactions with inhibitors of CYP3A4, such as the antifungal azole-derivatives itraconazole, ketoconazole and posaconazole.
- ▶ If treatment with an azole antifungal is indicated in a patient using a CYP3A4-metabolised statin, we recommend (1) topical administration of the antifungal agent, (2) the use of a non-CYP3A4-inhibiting antifungal drug such as terbinafine or (3) temporary discontinuation of statin treatment.

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