

## Case Report

# A CASE REPORT AND ROLE OF PHARMACIST ON DRUG-DRUG INTERACTION BETWEEN ATORVASTATIN AND ITRACONAZOLE

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## ABSTRACT

Although, the prescription of lipid lowering drugs, statin medication has increased globally and estimates suggest around 1.5 million people per year worldwide will experience myotoxicity related to statin use, but, its musculoskeletal side effects and their management strategy has not been highlighted in orthopaedic literature. The most commonly experienced side-effect of statin medication is muscle pain. Statin induced myopathy consists of a spectrum of clinical complications like myopathic disorders ranging from mild myalgia to fatal rhabdomyolysis. A case of 61 year old woman with a history of statin, atorvastatin with a triazole antifungal agent, itraconazole use presented with a 3 week history of progressive weakness of both shoulders and thighs. Symptoms progressed after a week of hospitalization. Therefore, it should be cautious to employ a drug holiday for the duration of antifungal therapy, choose a statin that does not have this interaction, or use another class of antifungal.

**Keywords:** Statin, Atorvastatin, Triazole Antifungal, Itraconazole, Myopathy

## INTRODUCTION

Estimates suggest around 1.5 million people per year worldwide will experience myotoxicity related to statin use (Sadasivam and Lecky, 2008). Most of the physician's prescriptions for geriatric population are with statins for the treatment of hypercholesterolemia (Shekar *et al.*, 2017), and they should be attentive in finding potentially serious drug-drug interactions between statins and azole antifungals. Hereby, report a case of myopathy resulting from the addition of itraconazole (CANDITRAL) to a stable medication regimen that included atorvastatin (ATORVA).

Before presenting the case, it is essential to know the definition of myopathy which can be defined in various ways. The National Lipid Association (NLA) defines myopathy as symptoms of myalgia in addition to an elevation in serum creatine kinase (CK) greater than 10 times the upper limit of normal (CK >10 × ULN).

The American College of Cardiology (ACC), American Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI) use myopathy as a general term referring to any disease of the muscles, which is the most common definition (Shekar *et al.*, 2017).

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Almost 4 billion prescriptions for medications were written in the United States in 2010, an all-time high in which more than 255.4 million prescriptions for statins and other lipid lowering drugs were filled (IMS Institute for Health Informatics, 2011).

Pfizer's Lipitor (atorvastatin calcium) was the highest selling branded statin. The 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, more commonly known as statins, are the most widely used medications for decreasing low-density lipoprotein (LDL) cholesterol. Statin use has been shown to decrease cardiovascular disease morbidity and mortality, but despite its advantages, over 40% of patients who have an indication for statin use are not receiving therapy. This may be secondary to a rare but major adverse event that is associated with the use of statins-myopathy (IMS Institute for Health Informatics, 2011).

### CASES

The patient is a 61-year-old woman with dyslipidemia, diabetes mellitus (DM), hypertension (HTN), and coronary artery disease (CAD). Her medications included atorvastatin 20mg (ATORVA), enalapril 5mg (NURIL), isosorbide dinitrate 10mg (SORBITRATE), atenolol 50mg (TENOSMIN), and biphasic isophane insulin (MIXTARD 30/70). Three weeks before presentation, she was prescribed itraconazole for fungal infection, tinea unguium. Two weeks after starting this medication, the patient presented to her physician with complaints of weakness in her arms and legs. Her symptoms were progressive, leading to the inability to walk without assistance. She was referred to the emergency medicine ward for further evaluation. Her examination was significant for upper and lower extremity proximal muscle weakness and the inability to rise from a sitting position. Laboratory tests revealed a total creatine kinase of 17,439 U per L and urine myoglobin of 130 mg per dL. Serum electrolytes and renal function were normal. Hepatic function revealed an aspartate transaminase of 805 U per L and alanine transaminase of 421 U per L. Hepatitis serologies were negative. Rheumatologic evaluation for myositis included antinuclear antibody screen, centromere antibody, rheumatoid factor, JO-1 autoantibody, SCL-70 autoantibody, all of which were negative. The patient was admitted for myopathy/ myalgia/ myositis/ rhabdomyolysis and was treated with intravenous hydration; urinary alkalization was not performed. During the seven-day hospitalization, the patient regained her baseline motor strength. The creatine kinase peaked at 20,740 U per L and then normalized. The hepatic transaminases also normalized, and the patient's renal function and urine remained normal. The patient was discharged and continues to follow with her primary physician.

### DISCUSSION

The statins: atorvastatin (ATORVAS), cerivastatin (LIPOBAY), lovastatin (LIPISTAT), and simvastatin (SIMVAS) are metabolized by the cytochrome P450 system, primarily CYP3A4. Pravastatin (PRAVACHOL) is not significantly metabolized and fluvastatin (LESCOL) is primarily metabolized by CYP2C9. Rosuvastatin (ROSUVAS) is excreted in the feces unchanged (90 percent), and the remainder undergoes metabolism by CYP2C9 (Williams and Feely, 2002).

The triazole antifungals: fluconazole (SYSCAN), itraconazole (CANDITRAL), ketoconazole (NIZORAL), and miconazole (MICOCEL) are potent inhibitors of CYP3A4 (Gubbins, 2011).

Inhibition of CYP3A4 results in markedly increased plasma statin levels, which increase the risk for myopathy. Atorvastatin and simvastatin have the greatest potential for this interaction (Bellosta *et al.*, 2004).

Since statins remain some of the most commonly prescribed pharmaceuticals, physicians are challenged to identify concomitant agents that inhibit their metabolism, namely CYP3A4 inhibitors. It is essential to health care provider to review the complete list of CYP3A4 and 2C9 substrates and inhibitors to minimize side effects and drug-drug interactions. As physicians are facing this issue, it should be cautious to employ a drug holiday for the duration of antifungal therapy, choose a statin that does not have this interaction, or use another class of antifungal.

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### Role of Pharmacists in Statin Therapy

- Pharmacists in the inpatient and outpatient setting may be directly involved in the monitoring of medication therapy and tolerability, and therefore should be aware of the signs and symptoms of statin-associated myopathy. Proper assessment of patients will assist in the recognition of patients at risk.
- Knowledge of the currently available statins and their properties will enable pharmacists to provide appropriate recommendations for individualized treatment regimens.
- Once patients are initiated on statin therapy, pharmacists have the opportunity to monitor patient adherence, treatment response, and medication safety, in addition to providing ongoing patient education on statin therapy and its adverse effects.
- Pharmacists should continue to counsel patients on the risk and warning signs of statin associated myopathy especially potential drug-drug interactions like statin-azole antifungals, as the incidence underscores the need for pharmacists to play a direct role in the monitoring of statin therapy in the inpatient and outpatient setting.
- Pharmacists can help in managing patients who take statins to ensure early identification of drug interactions or pharmacokinetic changes that might influence serum drug levels.

### REFERENCES

- Bellosta S, Paoletti R and Corsini A (2004).** Safety of Statins Focus on Clinical Pharmacokinetics and Drug Interactions. *Circulation* **109**[suppl III] III-50-III-57.
- Gubbins PO (2011).** Triazole antifungal agents drug-drug interactions involving hepatic cytochrome P450. *Expert Opinion on Drug Metabolism & Toxicology* **7**(11) 1411-29.
- Harper CR and Jacobson TA (2010).** Evidence based management of statin myopathy. *Current Atherosclerosis Reports* **12** 322-30.
- IMS Institute for Health Informatics.** The Use of Medicines in the United States: Review of 2010. Updated April 2011.
- Shekar HS, Rajamma AJ, Satheesha SB, Beere Nagaraju, Anil Kumar KV (2017).** Case Report: Simvastatin causing rhabdomyolysis- A case on drug-drug interaction. *Indian Journal of Hospital Pharmacy* **54**(3) 44-6.
- Sadasivam S and Lecky B (2008).** Statin induced myopathy. *British Medical Journal* **337** a2286.
- Shekar HS, Farnoud MG, Anil Kumar KV, Nagaraju B, Ravindran M and Ravi CM (2017).** Pharmacotherapeutic Benefits of Aspirin and Statins. *International Journal of Pharma Research and Health Sciences* **5**(2) 1627-31.
- Williams D and Feely J (2002).** Pharmacokinetic pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clinical Pharmacokinetics* **41** 343-70.