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Beware of Potential Drug Interactions With Coadministered Statins and Amiodarone

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Approximately 38.75 million adults in the United States are on cholesterol-lowering medications, most of whom are on HMG-CoA reductase inhibitors (statins).[1] Statins are used in the treatment of dyslipidemia and the primary and secondary prevention of cardiovascular disease (CVD). Most statins, such as simvastatin, atorvastatin, and lovastatin, undergo hepatic metabolism via cytochrome P450 isoenzyme 3A4 (CYP3A4). Fluvastatin and rosuvastatin undergo metabolism via CYP2C9. Of note, pravastatin and pitavastatin have no major cytochrome P450 metabolism.[2-5] When considering potential drug interactions with statin therapy, it is important to consider the hepatic pathways that could be negatively impacted with the addition of new medications. One such example of a potential drug interaction is the coadministration of statins with amiodarone.

MECHANISM OF DRUG INTERACTION

Amiodarone is a class III antiarrhythmic agent used in the treatment of atrial tachyarrhythmias and ventricular arrhythmias. This medication undergoes metabolism via CYP2C8 and CYP3A4, and it inhibits CYP450 isoenzymes 1A2, 2C9, 2D6, and 3A4. When amiodarone is given concomitantly with a statin that undergoes hepatic metabolism, the inhibition of the

metabolizing enzyme by amiodarone leads to an excess of statin. This increase in statin concentrations may lead to an increased risk of myopathy, hepatotoxicity, and rhabdomyolysis.

THE EVIDENCE

In 2014, Marot and colleagues[6] described the case of an 80-year-old man who had been on simvastatin, 40 mg daily, for 3 years with no adverse events. He presented to an emergency department with proximal pain and weakness in his lower extremities. Four days prior to presentation, he had received a diagnosis of atrial fibrillation for which amiodarone, 200 mg daily, had been initiated. Simvastatin was discontinued, and the man was asymptomatic by day 16. This case demonstrates the acute nature in which myopathies can present once this drug interaction has been introduced. Several other cases of this drug interaction have been reported.[7-9]

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial[10] evaluated whether 80 mg daily of simvastatin safely produces greater reductions in CVD risk than does 20 mg daily of simvastatin for secondary prevention of cardiovascular events. A subgroup analysis of participants who were receiving 80 mg of simvastatin found that participants who were also taking amiodarone had almost a 9-fold increase in the incidence of myopathy within the first year of therapy.

DISCUSSION

While this drug interaction can occur with any of the statins that undergo hepatic metabolism (**Table**), most reports in the literature cite specific interactions between amiodarone and simvastatin. This may be due to the fact that simvastatin is more susceptible to CYP3A4 inhibitors and has been on the market significantly longer than some of the other drugs in this class such as atorvastatin and rosuvastatin.

Table. Examples of Adverse Events Associated With Concomitant Statin and Amiodarone Use

Authors	Patient	Statin Dose	Amiodarone Dose	Clinical Presentation	Outcome
Marot et al[6]	80-year-old man	Simvastatin, 40 mg/d	200 mg/d	Proximal pain and weakness; creatine kinase, 29,760 U/L	Simvastatin discontinued and resolution of symptoms
Merz et al[12]	73-year-old woman	Rosuvastatin, 5 mg/d	200 mg/d	Elevated liver function test results	Rosuvastatin discontinued and resolution of symptoms
Ricaurte et al[8]	72-year-old man	Simvastatin, 80 mg/d	200 mg/d	Rhabdomyolysis, azotemia, possible hepatotoxicity; creatine kinase, 19,620 U/L	Both medications discontinued and resolution of symptoms

There are specific recommendations about simvastatin dosing when the medication is coadministered with amiodarone[10,11]; however, this should not lead to the belief that the interaction with amiodarone occurs only with simvastatin. Health care providers should remain

vigilant in monitoring drug interactions that could lead to serious adverse events such as myopathy, hepatotoxicity, and rhabdomyolysis with the coadministration of amiodarone and hepatically metabolized statins.

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