

Drug interactions

Drug interactions that can occur with statins and macrolide antibacterials

An elderly woman with a history of hyperlipidaemia and hypertension presents with a fast heart rate, and new-onset atrial fibrillation (AF) is diagnosed. Initial therapy with a beta blocker fails to control the AF, so diltiazem is prescribed. Aspirin is also started, and the patient's usual medication of ramipril 5mg daily and simvastatin 40mg daily is continued. A respiratory tract infection is also diagnosed, and so she is given a seven-day course of amoxicillin and clarithromycin. A week later she presents with fatigue, muscle weakness and dark urine, and on admission to hospital her creatine kinase level is 15,000units/L. A diagnosis of rhabdomyolysis is made, and the simvastatin is stopped.

Statins are commonly prescribed for the treatment of hyperlipidaemia and in the prevention of cardiovascular disease. Simvastatin is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4 and its metabolism may be significantly affected by drugs that can inhibit or induce CYP3A4. Drugs that are potent inhibitors of CYP3A4 can, therefore, lead to a large increase in simvastatin levels,

increasing the risk of developing serious adverse effects such as myopathy and rhabdomyolysis. Drugs that are moderate inhibitors of CYP3A4 can also increase the levels of these statins but have less effects than clarithromycin.

The patient in this case was taking both a potent and a moderate inhibitor of CYP3A4 (clarithromycin and diltiazem, respectively) with simvastatin 40mg daily. She should have been advised to omit her simvastatin while taking the clarithromycin. A maximum dose of simvastatin 40mg is advised when prescribed with diltiazem, so no dose adjustment is needed for this patient in the long term.

Other macrolides, such as erythromycin and telithromycin, are expected to interact with simvastatin in the same way as clarithromycin, because they are also moderate to potent inhibitors of CYP3A4. Simvastatin should also be temporarily stopped if these antibacterials are required. Azithromycin does not inhibit CYP3A4 and, therefore, would not be expected to interact with simvastatin.

Not all statins are metabolised in the same way as simvastatin. Atorvastatin is

metabolised by CYP3A4 but to a lesser extent than simvastatin. It can therefore interact with similar drugs, but usually to a lesser extent.

Fluvastatin, pravastatin and rosuvastatin are not significantly metabolised by CYP3A4 and are, therefore, are not expected to interact to a clinically relevant extent with CYP3A4 inhibitors. However, pravastatin levels have been reported to be moderately raised by clarithromycin and erythromycin, although the mechanism for this effect is not yet understood.

The Table illustrates the metabolic routes of the statins, and their interactions with the macrolide antibacterials.

Rarely, cases of rhabdomyolysis have been seen with pairs of statins and macrolides not expected to interact. Therefore, all patients taking statins should be counselled about the risks of myopathy. They should be encouraged to report any muscle pain, tenderness, or weakness, especially if accompanied by malaise, fever or dark urine. This warning should be reinforced if a CYP3A4-inhibiting macrolide is given concurrently.

	Azithromycin	Clarithromycin	Erythromycin	Telithromycin
Atorvastatin Partly metabolised by CYP3A4	No action	Max atorvastatin dose 20 mg daily	Omit drug during short-term antibacterial therapy if possible. If both are given start with a 10mg dose of atorvastatin	
Fluvastatin Mainly metabolised by CYP2C9	No action	No action	No action	No action
Pravastatin Not significantly metabolised by cytochrome P450	No action	Caution	Caution	Caution probably warranted
Rosuvastatin Less than 10% metabolised (by CYP2C9 and CYP2C19)	No action	No action	No action	No action
Simvastatin Mainly metabolised by CYP3A4	No action	Contraindicated Omit during short-term antibacterial therapy or consider alternative antibacterial		