

Drug interactions with statins

Statins are one of the most widely prescribed classes of medicines; in New Zealand over three million prescriptions were dispensed in 2012. Drug interactions may increase the risk of serious adverse reactions associated with statins, such as myopathy. Alarming, four Christchurch patients in a six-week period were recently admitted to hospital with serious myopathy (including one requiring ongoing dialysis) induced by drug interactions with simvastatin. This bulletin summarises important interactions with the three currently funded statins in New Zealand: simvastatin, atorvastatin and pravastatin.

Muscle toxicity

Myopathy is an uncommon but potentially fatal adverse reaction to statins. Statins are associated with three muscle syndromes:

- myalgia (pain without serum creatine kinase (CK) elevation)
- myositis (muscle pain with CK elevation)
- rhabdomyolysis (CK concentration >10 times the upper limit of normal (ULN) with worsening renal function).

The risk of myopathy in statin users is related to the drug concentration in the body; therefore, any drug interaction that results in a marked increase in statin concentrations can lead to toxicity and should be taken seriously.

Pharmacokinetics

Simvastatin: has high first-pass metabolism (via CYP3A enzymes) and very low bioavailability (<5%). If a patient is also taking a drug that inhibits CYP3A, the amount of systemic simvastatin can increase dramatically. Strong CYP3A inhibitors can increase simvastatin's bioavailability to 50%, resulting in up to 10-fold increases in plasma simvastatin concentrations. A number of drugs (e.g. ciclosporin) are also known to inhibit organic anion transporting polypeptide (OATP) which facilitates hepatic uptake of statins, thereby increasing plasma simvastatin concentrations.

In 2011 the US FDA:

- advised against using 80 mg doses of simvastatin
- added new drugs to those contraindicated with simvastatin
- included several new simvastatin dose limitations when prescribing with various interacting drugs.

These changes were based on analysis of the SEARCH study¹, which found the incidence of myopathy was 30 times higher

(0.03% vs. 0.9%) in patients taking simvastatin 80 mg compared with 20 mg. Furthermore, for each doubling of the simvastatin dose, there is only a small additional absolute reduction in cardiovascular events.

Atorvastatin: is also metabolised by CYP3A. However, in contrast to simvastatin, it has a higher bioavailability (15%), meaning that while CYP3A inhibitors will still increase atorvastatin plasma concentrations, the magnitude will be less than that seen with simvastatin. For example, clarithromycin, a strong CYP3A inhibitor, has been shown to increase systemic exposure of simvastatin by 10-fold; in contrast to atorvastatin, where the increase is around four-fold. Thus, despite both drugs being primarily metabolised by CYP3A, atorvastatin is less susceptible to CYP3A-based interactions than simvastatin.

Pravastatin: is not significantly metabolised by CYP enzymes; therefore, interactions based on this mechanism are unlikely. However, co-administration of OATP inhibitors may increase pravastatin concentrations. Although simvastatin or atorvastatin are generally used first-line in New Zealand, pravastatin should be considered in patients taking drugs which are likely to interact.

Pharmacodynamics

For any of these statins, co-administration with drugs which also cause myopathy will increase the risk of additive adverse effects.

Reference: 1. Lancet 2010;376(9753):1658-69

The table below highlights important drug interactions with simvastatin and atorvastatin.

Table: Important drug interactions with simvastatin and atorvastatin

Interacting drug	Simvastatin management	Atorvastatin management
Pharmacokinetic		
Strong CYP3A or OATP inhibition		
Aprepitant Azole antifungals ¹ Ciclosporin Danazol	Gemfibrozil Grapefruit juice Macrolide antibiotics ² Protease inhibitors ³	Avoid combination if possible (max dose 10 mg daily with ciclosporin)
Moderate CYP3A inhibition		
Amiodarone Cimetidine Ciprofloxacin Diltiazem	Fluconazole Montelukast Ticagrelor Verapamil	Avoid combination if possible (max dose 20 mg/day or 40 mg/day with ticagrelor)
CYP3A induction		
Carbamazepine Modafinil Nevirapine Phenobarbitone Phenytoin	Primadone Rifabutin Rifampicin St John's wort	Monitor for statin efficacy, increase in statin dose may be necessary
Pharmacodynamic		
Bezafibrate Colchicine	Fusidic acid Nicotinic acid (>1 g/day)	Max 10 mg/day with bezafibrate Max 20 mg/day with nicotinic acid Stop with fusidic acid (restart 7 days after last dose)
		Use with caution – consider dose reduction

1) Itraconazole, ketoconazole, posaconazole, voriconazole (fluconazole is a moderate CYP3A inhibitor)

2) Clarithromycin, erythromycin (roxithromycin and azithromycin are weak CYP3A inhibitors)

3) Atazanavir, boceprevir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir

Management

Any patient prescribed a statin should be told to promptly report signs of myopathy (unexplained muscle pain), especially if accompanied by malaise, fever or dark urine. For muscle pain without raised CK, reduce the statin dose or trial a different statin. If symptoms do not resolve, discontinuation may be required. If symptomatic with CK 3 to 10 x ULN; reduce the statin dose and monitor symptoms and CK weekly. If symptoms/CK do not normalise, statin discontinuation may be required. If there are symptoms and CK is elevated >10 x ULN, the statin should be discontinued immediately. Recent studies have found that some previously statin-intolerant patients may be able to tolerate rechallenge with a lower dose or a switch to an alternative statin.