

Simvastatin and atorvastatin: beware of potential CYP3A4 interactions when prescribing other medicines

Simvastatin and atorvastatin are the most frequently prescribed statins in New Zealand. Simvastatin, and to a lesser extent, atorvastatin, are metabolised by the hepatic isoenzyme CYP3A4. Medicines that inhibit or induce this enzyme (Table 1) are likely to affect the plasma concentration of these statins, resulting in either an increased risk of adverse effects (e.g. myopathy and rhabdomyolysis) or a reduction in the effectiveness of treatment.² For example, one study which investigated the effect of erythromycin (a potent CYP3A4 inhibitor) on serum simvastatin concentrations found that combined use resulted in a 6.2-fold increase in simvastatin exposure.¹

Other statins, e.g. pravastatin, are not significantly metabolised by CYP3A4 and are therefore less likely to have significant CYP enzyme interactions. However, caution is still required if prescribing any medicine that alters CYP3A4 with any statin as there have been case reports of interactions.^{1,3}

If a patient is using a combination of a CYP3A4 inhibitor and a statin, advise them to report any symptoms of myopathy and possible rhabdomyolysis, i.e. unexplained muscle pain, tenderness or weakness, especially in combination with dark coloured urine. If myopathy does occur, the statin should be stopped immediately.¹

Potent CYP3A4 inhibitors are contraindicated in people using simvastatin (Table 1). These include the macrolide antibiotics erythromycin and clarithromycin, azole antifungals and protease inhibitors used for HIV and hepatitis C. It is appropriate to stop using simvastatin or atorvastatin for a short time if the use of a potent inhibitor is required. For example, a patient can be advised to omit their simvastatin doses while completing a course of erythromycin, if there is no alternative.

Moderate CYP3A4 inhibitors include the calcium channel blockers, amlodipine, diltiazem and verapamil. When using simvastatin and moderate CYP3A4 inhibitors together, the dose of simvastatin should not exceed 20 mg per day (Table 1) and patients should be monitored for adverse effects. Atorvastatin may be used in conjunction with moderate CYP3A4 inhibitors with caution.

Minor CYP3A4 inhibitors, such as the macrolide antibiotics, azithromycin and roxithromycin, have only a minimal effect on simvastatin and atorvastatin levels. However, there have been isolated case reports of rhabdomyolysis when they have been used in combination with simvastatin.¹

CYP3A4 inducers include carbamazepine, rifampicin and St John's wort. These reduce the plasma concentration of simvastatin and atorvastatin and may reduce their effectiveness. If these medicines are used in combination with simvastatin and atorvastatin, lipid profiles should be monitored and the statin dose increased if necessary.

References:

1. Baxter K, Preston CL, (eds). Stockley's Drug Interactions [online]. London: Pharmaceutical Press, 2014. Available from: www.medicinescomplete.com (Accessed Apr, 2014).
2. Medsafe. Statins and CYP interactions. Prescriber Update 2014;35. Available from: www.medsafe.govt.nz (Accessed Apr, 2014).
3. New Zealand Formulary (NZF). NZF v20. 2014. Available from: www.nzf.org.nz (Accessed Apr, 2014).

Table 1: Examples of medicines that interact with simvastatin and atorvastatin (adapted from Prescriber Update, Medsafe²)

Interacting medicine	Simvastatin	Atorvastatin
Potent CYP3A4 inhibitors Erythromycin Clarithromycin Azole antifungals (e.g. itraconazole, posaconazole, voriconazole) Protease inhibitors (e.g. ritonavir, telaprevir, boceprevir) Gemfibrozil Ciclosporin Danazol	Combination contraindicated; use alternative or temporarily stop simvastatin for the duration of the treatment course	Avoid combination if possible but if required then use with caution and monitor for adverse effects, e.g. unexplained muscle pain, tenderness or weakness, especially in combination with dark coloured urine
Moderate CYP3A4 inhibitors Amiodarone Amlodipine Verapamil Diltiazem Nicotinic acid (> 1 g/day)	Do not exceed 20 mg/day	Use with caution and monitor for adverse effects (as above)
Minor CYP3A4 inhibitors Azithromycin Roxithromycin	Case reports of rhabdomyolysis. Use with caution and monitor for adverse effects (as above).	No clinically significant interactions
CYP3A4 inducers Carbamazepine Phenytoin Rifampicin St John's Wort	Probable reduction in plasma concentration of statin. Monitor lipid profile more regularly than usual for the patient.	Possible reduction in plasma concentration of statin. Consider monitoring lipid profile more regularly than usual for the patient.