LEADING ARTICLE

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Cytochrome P450 Drug Interactions Within the HMG-CoA Reductase Inhibitor Class

Are They Clinically Relevant?

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Abstract

The present review outlines the clinical relevance of pharmacokinetic drug interactions within the HMG-CoA reductase inhibitor class. These interactions can result in markedly increased or decreased plasma concentrations of some drugs within this class. However, the relationship between altered plasma concentrations and adverse effects or toxicity may not be linear. It is likely that other variables affect this concentration-effect relationship including: rapid changes in the concentration, concomitant lipid-lowering therapy or host genetic factors that code for different forms or amounts of metabolising enzymes and drug receptors.

It is not currently possible to predict which patients will manifest clinically important drug-drug interactions, nor what concentration of an HMG-CoA reductase inhibitor will cause rhabdomyolysis. Thus, until prescribers have better scientific information from which to develop a 'therapeutic range' for each agent, caution should be exercised. In particular, patients taking a CYP3A4-metabolised agent, e.g. atorvastatin, simvastatin and lovastatin, should not be started on a CYP3A4 inhibitor or inducer without close monitoring.

Pharmacokinetic drug interactions include all interactions between two or more agents that result in lowered or elevated concentrations of the reference drug. These agents may include internal substances such as endogenous hormones as well as external substances such as food or pharmaceuticals.

The most clinically relevant of the HMG-CoA reductase inhibitor interactions involve alterations in the metabolic pathways within the cytochrome P450 (CYP) system and in the phase II reaction of glucuronidation.

It is noteworthy that the HMG-CoA reductase inhibitors are not all metabolised in the same way. Some, e.g. atorvastatin, cerivastatin (now withdrawn; see section 3), simvastatin and lovastatin, are metabolised predominantly by the CYP3A4 enzyme. Cerivastatin is additionally metabolised by CYP2C8. Fluvastatin is metabolised by CYP2C9. Pravastatin is not metabolised by the CYP system to any significant extent, although it does undergo some metabolic alteration by phase II metabolic pathways in the liver.[1] Rosuvastatin is 90% excreted un-

Table I. Major metabolic pathways for HMG-CoA reductase inhibitors

	Major metabolic pathway
Rosuvastatin	Renal clearance
Atorvastatin	CYP3A4
Pravastatin	Phase II reactions in liver
Cerivastatin	CYP3A4
Fluvastatin	CYP2C9
Lovastatin	CYP3A4
Simvastatin	CYP3A4

CYP = cytochrome P450.

changed by the kidneys and the small amount of rosuvastatin that is metabolised (<10%) is done so via CYP2C9 and CYP2C19 (table I).[2]

Understanding the metabolic fate of HMG-CoA reductase inhibitors is important because it helps explain the reasons why particular drugs interact with some but not all HMG-CoA reductase inhibitors. Drugs that increase (by inducing) or reduce (by inhibiting) the metabolism of HMG-CoA reductase inhibitors can result in lower or higher concentrations of these drugs, respectively.

1. Effect of Additional Cytochrome P450-Mediated Drug Therapy on Plasma HMG-CoA Reductase Inhibitor Concentration

There are a number of pharmacokinetic reports describing the interaction between plasma concentrations of HMG-CoA reductase inhibitors and other commonly co-prescribed drugs. Most relate to drugs that inhibit or induce CYP3A4.

1.1 Diltiazem and Verapamil

The calcium antagonists diltiazem and verapamil are known CYP3A4 inhibitors. Diltiazem inhibits the metabolism of lovastatin, causing an increase in area under the serum concentration-time curve (AUC) and peak serum concentration (C_{max}), but does not interact with pravastatin.[3] Verapamil is a stronger inhibitor of the CYP3A4 enzyme than diltiazem, with concentrations producing 50% inhibition (IC_{50}) ranging from 4.8–5.6 μmol/L and 110–127 μmol/L, respectively when co-incubated with simvastatin.[4]

A randomised, double-blind crossover study was undertaken in 12 healthy volunteers to examine the effects of erythromycin 1.5 g/day, verapamil 240 mg/day or placebo, for 2 days, on the metabolism of simvastatin. On day 2, simvastatin 20mg was administered. Erythromycin and verapamil increased the C_{max} of simvastatin 3.4 times ($p < 0.001$) and 2.6 times ($p < 0.05$), respectively, and the AUC from time zero to 24 hours ($AUC_{0\text{-}24h}$) by 6.2 times ($p < 0.001$) and 4.6 times ($p < 0.01$), respectively. Erythromycin increased the mean C_{max} of active simvastatin acid by five times ($p < 0.001$) and the $AUC_{0\text{-}24h}$ by 3.9 times ($p < 0.001$). Verapamil increased the C_{max} of simvastatin acid 3.4 times ($p < 0.001$) and the $AUC_{0\text{-}24h}$ by 2.8 times ($p < 0.001$). As the co-administration of erythromycin or verapamil is common, the authors advise reducing the dosage of simvastatin by about 50–80% (at least when a simvastatin dosage >20 mg/day is used) when potent CYP3A4 inhibitors are administered.[5]

1.2 Itraconazole

Itraconazole is a pan-CYP enzyme inhibitor, although it inhibits the rate of CYP3A4-mediated reactions more than that of the other isoforms. Studies have been performed on healthy volunteers taking either placebo or itraconazole at steady state. Subjects were given atorvastatin,[6] simvastatin or pravastatin,[7] fluvastatin or lovastatin[8] in addition to itraconazole. Itraconazole increased the AUC of simvastatin almost 20-fold and the C_{max} just over 18-fold ($p < 0.001$ compared with placebo). Itraconazole increased the AUC of lovastatin 15-fold and increased C_{max} 11-fold ($p < 0.05$ compared with placebo), although it did not significantly affect the AUC or C_{max} of fluvastatin. This is likely to be because itraconazole has a higher apparent dissociation constant for CYP2C9 than for CYP3A4.

Itraconazole increased the AUC of atorvastatin almost 2-fold ($p < 0.001$) but did not significantly affect its C_{max}. It did not significantly alter the

AUC or C_{max} of pravastatin ($p = 0.052$ and 0.172, respectively).

1.3 Grapefruit Juice

Grapefruit juice is known to inhibit CYP3A4. This inhibition occurs to a much greater extent in the gut wall than in the liver but the end result is that increased concentrations of substances that are metabolised by CYP3A4 occur when taken with grapefruit juice.

In an non-blind, randomised, 2-phase, cross-over study, the interaction between grapefruit juice and lovastatin was studied by consumption of a single dose of lovastatin additional to either water or grapefruit juice.[9] Grapefruit juice increased the C_{max} for lovastatin 12-fold ($p < 0.001$) and the AUC for lovastatin 15-fold. An interaction has also been identified for simvastatin and grapefruit juice, with the latter increasing the C_{max} of simvastatin 9-fold ($p < 0.01$) and the AUC by 16-fold ($p < 0.05$).[10]

1.4 Mibefradil

An *in vitro* study demonstrated that mibefradil (now withdrawn; see section 2.2.1), a CYP3A4 inhibitor, inhibited the metabolism of simvastatin and lovastatin (metabolised by CYP3A4), but not pravastatin.[11]

1.5 Antidepressants

Many antidepressants are metabolised by and/or inhibit CYP3A4 (e.g. fluoxetine, fluvoxamine, nefazodone and sertraline). In addition, some are known to increase the concentration of several well-known drugs metabolised by CYP3A4.[12,13] It has been recommended by Davidson[14] that people taking a CYP3A4-metabolised HMG-CoA reductase inhibitor who subsequently require an antidepressant should be prescribed an antidepressant that does not inhibit or induce CYP3A4, such as paroxetine or venlafaxine.

Similarly, 2 weeks of treatment with the antidepressant hypericum (St John's wort) has been shown to significantly lower simvastatin AUC parameters by 52%, but not those of pravastatin. This is likely to be because hypericum induces CYP3A4, the enzyme that metabolises simvastatin.[15]

1.6 Protease Inhibitors

Nelfinavir (a CYP3A4 inhibitor) increases the AUC of atorvastatin by 122% and that of simvastatin by 505%.[16] As there are few other options for switching therapy when it comes to protease inhibitors, it has instead been suggested by Davidson[14] that when protease inhibitors are required, the HMG-CoA reductase inhibitor should be switched to a non-CYP3A4-metabolised agent such as fluvastatin or pravastatin.

2. Relationship of HMG-CoA Reductase Inhibitor Concentration to Efficacy and Toxicity

It is well documented that known CYP3A4 inhibitors inhibit and CYP3A4 inducers induce the metabolism of the CYP3A4-metabolised HMG-CoA reductase inhibitors such as lovastatin, atorvastatin, simvastatin and cerivastatin. However, this is only of clinical relevance if these altered concentrations result in either an increase in adverse effects or a loss of therapeutic effect.

2.1 Loss of Efficacy

The concentration of some CYP3A4-metabolised drugs such as cyclosporin and anti-HIV therapy may be reduced because of the co-administration of a CYP3A4-inducing drug, which may in turn lead to a subsequent loss of clinical efficacy.[17] This may also be the case with the CYP3A4-metabolised HMG-CoA reductase inhibitors, although this is not as well documented as the loss of efficacy is not usually immediately life-threatening. In addition, the prescriber response to reduced efficacy in this class is to attempt to increase the concentration by increasing the dose.

2.2 Increased Toxicity

As there have not been prospective dose-ranging studies of HMG-CoA reductase inhibitors with

measurement of the incidence of adverse effects such as elevated creatine kinase (CK), myositis or rhabdomyolysis, it is difficult to prove a definite cause-effect relationship with co-administration of a CYP3A4 inhibitor to a CYP3A4-metabolised HMG-CoA reductase inhibitor. Indeed rhabdomyolysis has occurred with small doses of relatively less potent HMG-CoA reductase inhibitors and does not always occur in people taking high doses of very potent HMG-CoA reductase inhibitors. In addition, the overall incidence of rhabdomyolysis is very low so establishing a putative relationship with plasma concentration is dependent on case reports in the literature or those submitted to the regulatory authorities. Such retrospective drug epidemiology has enabled the following links between dose, drug effect and plasma concentration.

2.2.1 Mibafredil

In 1997, the US FDA issued a warning label contraindicating the co-administration of mibefradil with lovastatin or simvastatin because both of these statins are metabolised by CYP3A4 and mibefradil inhibits this enzyme. The warning followed the receipt of seven reports of rhabdomyolysis in patients taking simvastatin and mibafredil concurrently, and the FDA also warned against the co-administration of both atorvastatin and cerivastatin with mibafredil following this. Mibafredil was voluntarily removed from the market in June 1998 because of 19 reported cases of rhabdomyolysis when given concurrently with simvastatin.[11]

2.2.2 Itraconazole

Rhabdomyolysis has been reported when simvastatin or lovastatin is co-administered with itraconazole.[7,18,19] One case involved a 74-year-old man taking lisinopril, aspirin and simvastatin 40 mg/day, and in whom itraconazole was later added for a dermatophytic infection. Three weeks later the patient developed leg, arm and neck pain. All drugs were stopped, but the patient developed brown urine, an elevated CK (22.8×10^6 U/L) and lactic dehydrogenase (927 000 U/L). Signs and symptoms started to resolve 36 hours following drug cessation.[20]

2.2.3 Diltiazem

A 53-year-old man taking a regimen of lovastatin, enalapril, nitrates and diltiazem developed signs and symptoms of myopathy after several months of taking these drugs, with a CK level of 4000 U/L and an electomyogram recording typical of myositis.[21] The symptoms settled 1 week after ceasing treatment. Treatment with lovastatin was then resumed with no recurrence of the symptoms. However, when diltiazem was reintroduced the myopathy (with elevated CK levels) recurred. Thus, the author concluded that the diltiazem-lovastatin drug interaction caused the rhabdomyolysis.

Diltiazem has been implicated in several cases of statin myopathy, although the absolute incidence of cases appears to be small. Among the 10 000 patients receiving simvastatin in the Heart Protection Study, 3000 were taking a calcium antagonist – the type was not specified but it is assumed from current practice trends that some of these would be taking diltiazem. Two cases of myopathy were reported in the simvastatin-treated group and one in the placebo-controlled group.[22]

2.2.4 Cyclosporin

A study investigating the incidence of rhabdomyolysis in 110 consecutive heart transplant patients receiving cyclosporin and HMG-CoA reductase inhibitors, 44 of whom received simvastatin (10–20 mg/day) and 66 pravastatin (20 mg/day) for at least 3 months, revealed no cases of rhabdomyolysis in the pravastatin-treated group. In the simvastatin-treated group, four patients had elevated CK.[23] In a similar Australian study, rhabdomyolysis occurred only in simvastatin-treated patients in a group of 87 heart transplant patients who received simvastatin or pravastatin in addition to cyclosporin.[24]

A case report of a renal transplant patient receiving cyclosporin and simvastatin described the development of rhabdomyolysis after the addition of clarithromycin for a soft tissue infection.[25] The higher concentrations of cyclosporin and simva-

statin as a result of concomitant clarithromycin were concluded to be the cause.

There have been numerous other cases of myopathy and elevated systemic exposure of HMG-CoA reductase inhibitors in transplant patients taking cyclosporin and HMG-CoA reductase inhibitors concurrently.[26-28] Fluvastatin and pravastatin are documented as having a lower propensity for myopathy in cyclosporin-treated patients because they are metabolised predominantly by enzymes other than CYP3A4. Cyclosporin has been shown to increase both the AUC of pravastatin as well as of fluvastatin by 5–23 times and C_{max} by 8.[29-31] While no clinical studies have shown a serious myopathy or rhabdomyolysis in cyclosporin- and pravastatin-treated subjects, postmarketing data has examined case reports of this occurrence.[32] The mechanism is purported to be that of alterations in biliary excretion, which may be affected by cyclosporin-induced cholestasis,[33] or an interaction involving transporter proteins such as P-glycoprotein.[34]

2.2.5 Erythromycin

A 68-year-old woman, administered lovastatin for hypercholesterolaemia, was admitted to hospital for evaluation of dyspnoea and pulmonary infiltrates. She had previously been treated with amoxicillin-clavulanic acid. Her antibacterial therapy was changed to a 10-day course of erythromycin and 5 days after completing this, she experienced muscle weakness and tenderness, developed dark urine and her CK levels reached 26 400 U/L. Lovastatin was discontinued, but a lovastatin plasma concentration taken 2.5 hours after the last dose of lovastatin showed a concentration almost three times higher than normal at 48 nmol/ml. The elevated lovastatin plasma concentration was documented as the cause of the rhabdomyolysis and fatal renal failure.[35]

Two similar case of rhabdomyolysis have been reported: one in a patient with renal insufficiency who was treated with the same combination;[36] and a second induced by a short course of erythromycin in a patient taking cyclosporin and lovastatin.[26] In a review, a 50-fold increase in lovastatin-induced myopathy (0.1–5%) has been reported when this agent is co-administered with erythromycin.[37]

2.2.6 Nefazodone

Myositis and rhabdomyolysis (CK 6081 U/L) developed in a man taking simvastatin 40 mg/day for 19 weeks, 4 weeks after he commenced nefazodone 200 mg/day for depression.[38] Values returned to normal 3 weeks after stopping both the simvastatin and the nefazodone. The authors speculated that the nefazodone had altered the metabolism of simvastatin through CYP3A4 inhibition, causing increased simvastatin concentrations and subsequently rhabdomyolysis.

3. Clinical Sequelae of HMG-CoA Reductase Inhibitor Drug Interactions

Many of the above cases involve pharmacokinetic interactions only. However, because of the magnitude of the effect seen, and the possible relationship between increasing plasma concentration and adverse effects, authors of these studies have advised prescribers to change drugs if possible, or to alter the dose. For some drugs this is difficult, as the effect is not predictable. For example, regarding the grapefruit juice interaction, it would be straightforward to warn patients taking a CYP3A4-metabolised HMG-CoA reductase inhibitor to reduce the dose by a standard amount when taking grapefruit juice. However, in practice this is difficult because the amount of furanocoumarin in grapefruit juice (which causes inactivation of CYP3A4) differs in different brands of grapefruit juice. Thus, the effect does not have the predictability to allow a safe and effective reduction in the dose. The authors of the grapefruit study recommend that the safest precaution for patients who drink grapefruit juice intermittently is to switch to a HMG-CoA reductase inhibitor that does not require CYP3A4 for metabolism. Davidson[14] advises drinking orange juice rather than grapefruit juice or separating the administration of the CYP3A4-metabolised HMG-CoA reductase inhibitor and grapefruit juice by at least 2 hours. In addition, some patients have more CYP3A4 than

others as a result of genetics. Thus, in some patients with small amounts of CYP3A4, inhibiting the CYP3A4 they do have would result in a marked reduction in clearance of a highly CYP3A4-metabolised drug.

Adverse effects have occurred with therapeutic doses and in all HMG-CoA reductase inhibitors, regardless of whether concurrent CYP-interacting agents are co-administered. Indeed, rhabdomyolysis from all HMG-CoA reductase inhibitors as monotherapy has been reported to the regulatory authority in Australia, although the incidence is low. There is a low incidence of simvastatin-induced rhabdomyolysis in large-scale trials. In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial[39] (n = 9014), West of Scotland Coronary Prevention Study (WOSCOPS)[40] (n = 6595) and Cholesterol and Recurrent Events (CARE)[41] studies (n = 4159), data on >112 000 person-years of exposure in double-blind randomised trials comparing placebo with pravastatin (40mg once daily) were collected. The percentage of patients with any abnormal liver function test after baseline sampling was similar (>3 times the upper limit of normal [ULN] for alanine aminotransferase: 128 patients [1.4%] for pravastatin vs 131 [1.4%] for placebo). Study medication was withdrawn in three pravastatin and seven placebo recipients because of creatine phosphokinase elevations, and no cases of mild or severe myopathy were reported. A Cox regression model indicated that the likelihood of discontinuing pravastatin was less than placebo.[42]

The Heart Protection study examined 20 536 patients with coronary disease, other occlusive arterial disease, or diabetes mellitus who were randomly allocated to simvastatin 40mg daily or placebo during a 5-year study period.[22] In the simvastatin-treated group, 5 of the 10 269 subjects (0.05%) developed myopathy (defined as muscle symptoms plus CK above 10 × ULN) compared with 1 in 10 267 (0.01%) of the placebo-treated group (p = 0.2). Interestingly, only 0.05% of simvastatin recipients developed rhabdomyolysis (CK >40 × ULN) compared with 0.03% of placebo recipients. Persistent elevation of CK (4 × ULN) was found in 0.07% of the simvastatin-treated group compared with 0.01% of the placebo-treated group (p = 0.07). There was no significant difference between the two groups in the numbers of subjects whose study treatment was stopped because of muscle symptoms (0.5% in each group). Thus, the annual excess risk of myopathy with 40mg simvastatin was low (0.01% in this study). Unfortunately, similar data of the magnitude of that available for simvastatin, pravastatin and lovastatin are not yet available for the three synthetic HMG-CoA reductase inhibitors fluvastatin, atorvastatin and cerivastatin.

The unfortunate experience of cerivastatin supports the fact that unexpected serious adverse events that are rare (as in the case of rhabdomyolysis) may not be detected until a large number of patients have been exposed for a long period of time. Cerivastatin was withdrawn from the market in 2001 due to 52 deaths attributable to the drug. Factors that increased the risk were high dose of cerivastatin and concomitant gemfibrozil.[43] It is encouraging that results of several large trials with the synthetic HMG-CoA reductase inhibitors will soon be available.

4. Mechanism of Toxicity

Rhabdomyolysis appears to be, at least partially, related to the degree of cholesterol lowering, which is in turn related to dose[44,45] and plasma concentration[37,45] as well as concomitant lipid-lowering therapies. The exact mechanism is unknown, but has been suggested to be related to reductions in ubiquinone (demonstrated for atorvastatin and lovastatin[45]), an important part of the cell replication pathway and synthesised from mevalonic acid. This leads to an unstable action potential in the muscle and disruption of the muscle cell membrane. Reductions in ubiquinone are a result of reductions in mevalonic acid levels by the HMG-CoA reductase inhibitors.

There are three properties of HMG-CoA reductase inhibitors that could affect mevalonic acid levels. The first is related to the different potency of the HMG-CoA reductase inhibitors. Thus,

higher potency HMG-CoA reductase inhibitors (such as cerivastatin) reduce the mevalonic acid level with a smaller amount of drug. Secondly, higher concentrations of HMG-CoA reductase inhibitors (from increased dose, inhibited clearance or from addition of other hypolipidaemic drugs) could reduce mevalonic acid levels in a direct concentration-effect relationship. Indeed, examining the recent case reports of rhabdomyolysis with cerivastatin, higher doses did appear to be linked to rhabdomyolysis. Undoubtedly, differences in amounts of interindividual CYP proteins and concomitant CYP3A4 inhibitors or inducers are important in contributing to elevated concentrations for those patients taking a CYP3A4-metabolised HMG-CoA reductase inhibitor. Thirdly, HMG-CoA reductase inhibitors with hydrophobic properties (i.e. simvastatin and lovastatin) may more easily permeate the muscle membrane than the hydrophilic drugs such as pravastatin.[45] This may explain why there appears to be a difference in propensity to cause rhabdomyolysis across the HMG-CoA reductase inhibitor class, and why the incidence is higher with concurrent fibrate therapy.

In the specific instance of the increase in reported cases of severe rhabdomyolysis with the combination of cerivastatin and gemfibrozil, metabolic interactions did appear to play a dominant role. Gemfibrozil is an inhibitor of both CYP2C9 and CYP2C19, enzymes that are involved in the metabolism of some of the HMG-CoA reductase inhibitors.[46] More recently, gemfibrozil has been shown to inhibit simvastatin, atorvastatin and cerivastatin acid glucuronidation (the pathway for elimination of the active hydroxy acid metabolites of simvastatin, atorvastatin and cerivastatin, respectively) by inhibiting uridine diphosphate-glucuronosyl transferase enzymes.[47] In addition, gemfibrozil, although not inhibiting CYP3A4, does inhibit the CYP2C8-mediated oxidative metabolism of cerivastatin.[48] These findings are in accordance with the clinical data that suggested an increase in incidence of rhabdomyolysis with the specific fibrate gemfibrozil and the specific HMG-CoA reductase inhibitor, cerivastatin.

In contrast to CYP3A4-metabolised HMG-CoA reductase inhibitors, the pravastatin-fibrate combination has not been associated with severe myopathy. In a double-blind, placebo-controlled study, 290 patients were randomised to receive either pravastatin (40 mg/day), gemfibrozil (1200 mg/day), pravastatin and gemfibrozil, or placebo for 12 weeks.[48] The study reported a low incidence of myopathy for the pravastatin-gemfibrozil combination (4/75 had CK abnormalities compared with 1/73 in the placebo group), although it is noted that this was only a 12-week study.

5. Conclusions

All HMG-CoA reductase inhibitors given as monotherapy can cause rhabdomyolysis. However, the incidence appears to be increased by a number of additional factors. These include high concentrations of a HMG-CoA reductase inhibitor or concomitant fibrate therapy, both of which cause a greater reduction in cholesterol, a necessary component of muscle membranes.

High plasma concentrations can occur for a number of reasons. Drug-drug interactions between the HMG-CoA reductase inhibitors atorvastatin, simvastatin, cerivastatin and lovastatin and CYP3A4 inhibitors can lead to elevated concentrations of these HMG-CoA reductase inhibitors. However, pravastatin is not substantially metabolised by CYP3A4 and addition of CYP3A4 inhibitors has not been shown to elevate plasma concentrations of this drug. Interindividual variation in CYP3A4 means that some patients are effectively on a CYP3A4 inhibitor before they start the HMG-CoA reductase inhibitor. Unfortunately, it is not possible, at least in the short-term, to mass genotype all patients for their cytochrome P450 status prior to starting therapy.

It is also not currently possible to predict which patients will manifest clinically important drug-drug interactions, nor what concentration of a HMG-CoA reductase inhibitor will cause rhabdomyolysis. It is this unpredictability that emphasises the need for caution. Until prescribers have better scientific information from which to de-

velop a 'therapeutic range' for each HMG-CoA reductase inhibitor, caution should be exercised. In particular, patients taking a CYP3A4-metabolised HMG-CoA reductase inhibitor should not start taking a CYP3A4 inhibitor or inducer without close monitoring.

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