## Studying the statins

There are several inaccuracies in Robert Herman's review of the statins.[1] First, he listed several inhibitors of cytochrome P-450 (CYP), including diltiazem and substances found in grapefruit juice and green tea, and labelled them all "potent inhibitors." Calcium-channel blockers have not been associated with an increase in myopathy in either controlled clinical trials or clinical practice.[2] Grapefruit juice, when taken in normal quantities in the morning, has minimal effects on the serum concentration of HMG–CoA reductase inhibitors following administration of lovastatin and has not been shown to have any clinically significant adverse effects.[3]

Second, Herman singled out lovastatin and simvastatin as being particularly likely to cause drug interactions by implying that active metabolites play no significant role. He noted that atorvastatin and cerivastatin are at least partially exonerated because "active ... metabolites of atorvastatin and cerivastatin contribute in large measure to their overall clinical activity." He concluded, "Thus, inhibition of first-pass metabolism of lovastatin and simvastatin could result in 10–20 fold elevations (oral availability increasing from 5% to 100%) in steady-state concentrations with a marked liability to drug toxicity." This is also inaccurate. Approximately 75% of the HMG-CoA reductase inhibitory activity of simvastatin results from 3 active metabolites. Therefore, measuring only the parent compound, such as simvastatin, grossly overestimates the overall interaction with CYP inhibitors.[2]

Editorialists Lori Shapiro and Neil Shear highlighted the statins as an example of a drug class in which not all members share similar drug interactions.[4] They stated, "To date, all reports of significantly increased rates of myalgia in patients receiving combination therapy with a statin and certain other agents involve simvastatin or lovastatin, the statins with the highest known metabolic dependency on the CYP3A4 pathway for elimination." This is simply not true; several cases of myopathy have been reported in patients taking pravastatin concomitantly with cyclosporine.[2] In addition, a significant increase in creatine kinase was documented in a patient taking nefazodone and pravastatin concomitantly, necessitating the discontinuation of nefazodone.[5]

Simvastatin has been well tolerated by millions of patients and has been shown to decrease coronary mortality by 42% in patients with high cholesterol levels and heart disease. Some drugs, such as niacin, fibrates and cyclosporine, increase the likelihood of myopathy with all statins. Other drugs, such as erythromycin, clarithromycin, the azole antifungals, nefazodone and other HIV protease inhibitors, increase the potential for myopathy when given concomitantly with statins metabolized by CYP3A4.

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### [The author responds:]

The metabolism and action of simvastatin (and lovastatin) are complex.[1] The parent drug is without intrinsic activity. However, it is readily metabolized to simvastatin acid by nonenzymatic hydrolysis as well as by nonspecific esterases in the liver and other tissues. It is also metabolized through a parallel pathway by hepatic and intestinal CYP3A4. The fact that the CYP3A4 metabolites circulate in blood in much higher concentrations than simvastatin acid has led to speculation that they may account for as much as 75% of the overall HMG–CoA reductase inhibitory activity of the drug. However, simvastatin acid and other open-lactone metabolites are also capable of undergoing reversible lactonization in tissues and exist in an equilibrium between active acid and inactive lactone forms. The lactone forms, including the parent simvastatin, have partition coefficients of around 4.7. In animal experiments, myopathy has been linked to the more lipophilic derivatives.[2] Thus, the inactive lactones may be important in the distribution of the drug into tissues, where they are subsequently metabolized and have their effects on cells.

Inhibition of CYP3A4 results in a shift in simvastatin metabolism away from the hydroxylated metabolites toward simvastatin and simvastatin acid. This always produces a more lipid-soluble and more active drug–metabolite profile. The question is, by how much? One can measure the absolute levels of drug and metabolites in blood by quantitative chromatography or by the activity profile of mixed active and inactive drug using a bioassay. I quoted[3] the changes in simvastatin acid induced by itraconazole (19-fold), a potent CYP3A4 inhibitor, from a well-designed placebo-controlled crossover study.[4] In Ernest Prégent's opinion, the bioactivity profile (5.2-fold[4]) would have been more appropriate. One could argue that estimation of bioactive equivalent concentrations may be confounded by high levels of inactive metabolites in the presence of an inhibitor, or that bioactivity does not reflect differences in plasma protein binding or lipophilicity for mixtures of substrates. However, neither the quantitative nor bioassay method tells us unequivocally what is happening in the cell.

In my article I tried to emphasize the characteristics of a drug that may predispose it to a potentially serious drug interaction. Dose-dependent toxicity within or close to the therapeutic range and high first-pass metabolism are clearly associated with HMG–CoA

reductase inhibitors. Partly to make a teaching point regarding balanced inhibition and partly because of clinical interest in the drug, I tried to moderate these concerns with atorvastatin. In this case, there is a 1:1 relation between the active parent drug and the active hydroxy metabolites; the metabolites are as potent as or slightly more potent than atorvastatin itself; the differences in lipophilicity are much less than those with simvastatin; and the changes in concentration (a 3.3-fold increase in atorvastatin acid, a 1.6-fold increase in bioactivity) are within the usual dosing ranges for the drug.[5] One could not make the same concessions for simvastatin or lovastatin.

The issue regarding the interaction of calcium-channel blockers and statins has been addressed by others.[6] There is a major interaction (3.5–6.2 fold elevations in statin concentration) between diltiazem or verapamil and lovastatin or simvastatin.[7,8] The change in drug levels is about the same order of magnitude as the interaction of these drugs with erythromycin. Prégent would like us to believe that a recently published meta-analysis[9] adequately addresses concerns regarding concomitant use of these drugs with the statins and that their interactions are without clinical significance. However, these data came from studies designed to assess clinical efficacy and not adverse events, least of which would be drug interactions. There were no controls of the number or types of potential inhibitors used by patients (they reported aggregate data for calcium-channel blockers) and the numbers of events were far below those that would be required to show a difference, if any existed. In other words, the data are poor and are vastly underpowered to answer the question.

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**[The editorialists respond:]**

We thank Ernest Prégent for his comments about our editorial.[1] He is correct to point out that not all reports of significant rates of myalgia in patients receiving combination therapy with a statin and certain other agents have involved simvastatin or lovastatin. However, the reports with these particular HMG–CoA reductase inhibitors are often based mechanistically on their inhibition by a CYP3A4 inhibitor. The concept of differential susceptibility of the statins in terms of CYP3A4 inhibition still holds true.

The myopathy reported in patients receiving combination therapy with pravastatin and cyclosporine clearly is not based on inhibition of CYP3A4 metabolism. We all continue to learn as these drugs are used, and therefore interactions are often not recognized until years after clinical trials are completed. Adverse reports of large trials such as those discussed by Gruer and colleagues[2] are reassuring. However, the data do have limitations. This study was conducted when our understanding of cytochrome-mediated drug metabolism was in the early stages. Therefore, drug interactions may have been underrecognized. While the mechanism of cyclosporine–pravastatin interactions is not known, it could relate to interference with transport mediated by P-glycoprotein.[3]

We know that a few drugs, such as niacin, fibrates and cyclosporine, increase the likelihood of myopathy with *some*, not *all* statins as Prégent states. In the end, we all agree that the potential for myopathy increases when the most potent CYP3A4 inhibitors are given with statins metabolized by CYP3A4.

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