

Long-term Safety of Hepatic Hydroxymethyl Glutaryl Coenzyme A Reductase Inhibitors

The Role of Metabolism—Monograph for Physicians

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The hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors (HMGs) have an excellent safety profile.^{1,2} Each of the 6 members of this therapeutic class (lovastatin,³ simvastatin,⁴ pravastatin,⁵ fluvastatin,⁶ atorvastatin,⁷ and cerivastatin⁸) has a low risk (<1%) of adverse drug reactions (ADRs). Nevertheless, some differences in safety have emerged within this category. The physicochemical properties of the HMGs may have important clinical implications. There are metabolic differences among the 6 available HMGs that may translate into significant differences in long-term safety.

Two of the ways that physicians help to ensure the safety of their patients is by prescribing agents that minimize the risk of ADRs, especially those caused by drug-drug interactions, and by counseling patients about potential drug interactions associated with HMG therapy. Therefore, it is important for physicians to understand the differences among the HMGs with regard to safety. The objectives of this review are to provide an overview of the pharmacokinetic properties of the HMGs, to discuss the role of cytochrome P450 (CYP450) isoforms in drug metabolism, to explain differences in metabolism among the HMGs, to review drug interaction studies dealing with the HMGs, to present case reports dealing with HMG-related myopathy, and to discuss major clinical implications of these case reports.

PHYSICOCHEMICAL AND PHARMACOKINETIC DIFFERENCES

The differences in the chemical structures of the HMGs may have several ramifications. Pravastatin is a hydrophilic compound, whereas the other HMGs are lipophilic^{2,9} (**Table 1**). Lipophilic compounds are metabolized to more hydrophilic compounds for excretion, whereas

hydrophilic compounds are more likely to be excreted in the urine as unchanged drug, thus reducing the potential for drug-drug interactions.

There are some noteworthy pharmacokinetic differences among the various HMGs (Table 1). Atorvastatin has the longest half-life (11-14 hours), whereas the half-lives of the other HMGs range between 1.2 and 3 hours.² When an ADR occurs, a long half-life can extend the duration of the adverse effect. For example, the mean elimination half-life of terfenadine is 16.4 hours.¹⁰ Thus, there is the potential that the rate-corrected QT interval prolongations and ventricular arrhythmias that may occur when terfenadine is coadministered with interacting drugs (eg, ketoconazole and erythromycin) may persist for a considerable period.

There are also differences in protein-binding characteristics. Pravastatin is approximately 50% protein bound, whereas the other HMGs are more than 95% protein bound.² Extensive protein binding may occasionally cause drug interactions by displacing other highly protein-bound agents, resulting in increased concentrations of free, active drug. The clinical importance of the protein-binding interactions of the HMGs has not yet been determined. There are also differences related to the ways and the extent to which the different HMGs are metabolized.

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Table 1. Summary of Key Pharmacokinetic Properties* of the HMGs†

| Pharmacokinetic Parameter | Lovastatin | Simvastatin | Pravastatin | Fluvastatin | Atorvastatin | Cerivastatin |
|---------------------------|------------|-------------|-------------|-------------|--------------|--------------|
| Lipophilic | Yes | Yes | No | Yes | Yes | Yes |
| Elimination half-life, h | 3 | 2 | 1.8 | 1.2 | 14 | 2 |
| Protein binding, % | >95 | 95-98 | ~50 | >98 | 98 | >99 |
| Active metabolites | Yes | Yes | No | No | Yes | Yes |
| Metabolized via CYP450 | Yes | Yes | NS* | Yes | Yes | Yes |

* See White and Chow² and Hamelin and Turgeon.⁹

†HMG indicates hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitor; NS, not clinically significant; and CYP450, cytochrome P450.

THE ROLE OF THE CYP450 SYSTEM IN DRUG METABOLISM

Most drugs undergo substantial metabolism,¹¹ a process that makes drugs more water soluble and thus more easily excreted in the urine or bile.¹² Many drugs, including the HMGs, undergo phase I metabolism by enzymes in the liver and sometimes in the gut wall, producing metabolites that are either eliminated by the kidneys or further metabolized and then excreted.^{11,13} Some of these metabolites may have pharmacological activity similar to that of the parent compound. A few drugs undergo phase II metabolism, being directly conjugated without undergoing the prior enzymatic biotransformation characteristic of phase I metabolism.¹¹

The most important group of phase I enzymes are the members of the CYP450 superfamily.¹⁴ These enzymes are found chiefly in hepatocytes, although they also occur in small-intestine enterocytes and, to a lesser extent, in the kidneys, lungs, brain, and other parts of the body.¹⁵ Cytochrome P450 enzymes are called isoforms because each derives from a different gene.¹² More than 30 human CYP450 isoforms have been identified, but CYP3A4, 2C9, 1A2, and 2D6 are responsible for most drug metabolism.

In terms of their metabolic properties, drugs can be classified as substrates, inhibitors, and inducers. The substrate is the drug metabolized, and thus may be called the object drug.¹¹ Inhibitors and inducers, which are usually lipophilic, are often referred to as precipitating drugs.^{11,15} When a drug that is metabolized via CYP450 (substrate) is taken with an agent that

decreases the activity (inhibitor) of that enzyme, the result may be an increase in the concentrations of the substrate that can increase the potential for an ADR. Because most drugs are metabolized to inactive or less active metabolites in the body, inhibition of this process by other medications can increase the pharmacodynamic effect of one or both of these drugs. This is one of the most common ways in which clinically important drug interactions occur.

Cytochrome P450 activity is highly variable from patient to patient, with at least a 10-fold inter-subject variability in activity documented for CYP3A4.¹¹ These differences may increase the sensitivity to drug interactions involving CYP450 competition in patients with low or nonexistent activity of a specific isoform, and helps explain why the same drug-drug combination is toxic to some but not all patients. For example, approximately 8% of Americans lack the gene that forms the CYP2D6 isozyme.¹¹ Because many cardiovascular and psychotropic drugs are metabolized by 2D6, these patients are at increased risk for drug toxic effects.

The CYP3A4 isoform metabolizes the greatest number of drugs and endogenous substances in humans.¹⁵ It accounts for 60% of CYP450 enzymes in the liver and 70% of cytochrome enzymes in gut wall enterocytes. Among the commonly used drugs that are metabolized by CYP3A4 are certain antibiotics, calcium channel blockers, antidepressants, immunosuppressants, HMGs, benzodiazepines, antihistamines, and protease inhibitors (**Table 2**).

Cytochrome P2C9 is involved in the metabolism of many nonsteroi-

dal anti-inflammatory drugs, phenytoin, tolbutamide, and S-warfarin (**Table 3**). Drugs that substantially inhibit the metabolism of one CYP2C9 substrate (eg, phenytoin) can be expected to inhibit the metabolism of other 2C9 substrates as well (eg, tolbutamide or S-warfarin).¹⁶ Unlike other HMGs, fluvastatin is substantially metabolized by CYP2C9. In addition to being a 2C9 substrate, fluvastatin may also act as a 2C9 inhibitor, probably on a competitive basis.

Cytochrome P2D6 is involved in the metabolism of many cardiovascular and psychotherapeutic drugs.¹¹ Major 2D6 substrates are codeine, desipramine, dextromethorphan, haloperidol, hydrocodone, metoprolol, thioridazine, and tramadol. Inhibitors include amiodarone, cimetidine, fluoxetine, paroxetine, propoxyphene, quinidine, and thioridazine. Cytochrome P2D6 is responsible for the conversion of codeine to morphine, a process that seems necessary for codeine activity. Approximately 8% of Americans are genetically deficient in CYP2D6, and many others are taking potent 2D6 inhibitors such as fluoxetine, paroxetine, and quinidine. Thus, it is likely that between 10% and 20% of the population will not adequately respond to codeine.

OVERVIEW OF HMG DRUG METABOLISM: FOCUS ON CYP450 ISOFORMS

There are differences related to the ways that HMGs are metabolized and the extent to which they are metabolized. These differences have important ramifications for patients and physicians because substantial CYP450 metabolism increases the likelihood that a drug-drug interaction will occur when an HMG metabolized by this isoform is given concomitantly with one or more agents competing for the same pathway. Clinically significant drug interactions can occur when drugs metabolized by the same isoform are taken concomitantly. Inhibition of CYP3A4 can produce severe toxic effects.¹¹ Cardiac arrhythmias have occurred with astemizole, terfenadine, and

Table 2. Representative List of Commonly Used Drugs Metabolized by Cytochrome P3A4: Substrates, Inhibitors, and Inducers*

| Substrates | Inhibitors | Inducers |
|--------------------------------|---------------------|---------------------|
| Alfentanil | Lidocaine | Carbamazepine |
| Alprazolam | Loratadine | Dexamethasone |
| Astemizole | Losartan | Ethosuximide |
| Atorvastatin | Lovastatin | Phenobarbital |
| Calcium channel blockers | Mibefradil | Phenytoin |
| Cannabinoids | Miconazole | Primidone |
| Carbamazepine | Midazolam | Rifabutin |
| Cerivastatin | Neavelbine | Rifampin |
| Cisapride | Nefazodone | Troglitazone |
| Clindamycin | Ondansetron | |
| Clomipramine | Paclitaxel | |
| Clonazepam | Prednisone | |
| Cocaine | Protease inhibitors | |
| Cyclophosphamide | Quinidine | |
| Cyclosporine | Rifampin | |
| Dexamethasone | Sertraline | |
| Diltiazem | Sildenafil | |
| Doxorubicin | Simvastatin | |
| Ergotamine | Tracolumus | |
| Erythromycin | Tamoxifen | |
| Estrogens, oral contraceptives | Terfenadine | |
| Ethinyl estradiol | Triazolam | |
| Etoposide | Verapamil | |
| Fentanyl | Vinblastine | |
| Felodipine | Vincristine | |
| Imipramine | R-Warfarin | |
| Ketoconazole | Zileuton | |
| | | Amiodarone |
| | | Cannabinoids |
| | | Clarithromycin |
| | | Cyclosporine |
| | | Danazol |
| | | Delavirdine |
| | | Diltiazem |
| | | Erythromycin |
| | | Fluconazole |
| | | Fluoxetine |
| | | Fluvoxamine |
| | | Grapefruit juice |
| | | Indinavir |
| | | Itraconazole |
| | | Ketoconazole |
| | | Omeprazole (slight) |
| | | Metronidazole |
| | | Mibefradil |
| | | Miconazole |
| | | Nefazodone |
| | | Nelfinavir |
| | | Norfloxacin |
| | | Propoxyphene |
| | | Quinine |
| | | Ritonavir |
| | | Saquinavir |
| | | Sertraline |
| | | Troleandomycin |
| | | Verapamil |
| | | Zafirlukast |

*See Hansten¹¹ and Michalets.¹⁵

Table 3. Representative List of Commonly Used Drugs* Metabolized by Cytochrome P2C9: Substrates, Inhibitors, and Inducers†

| Substrates | Inhibitors | Inducers |
|-------------|-------------------|---------------|
| Diazepam | Amiodarone | Carbamazepine |
| Diclofenac | Azole antifungals | Phenobarbital |
| Fluvastatin | Chloramphenicol | Phenytoin |
| Ibuprofen | Cimetidine | Rifampin |
| Losartan | Fluoxetine | |
| Naproxen | Fluvastatin | |
| NSAIDs | Fluvoxamine | |
| Phenytoin | Metronidazole | |
| S-Warfarin | Omeprazole | |
| Tolbutamide | Ritonavir | |
| Torsemide | Sulfaphenazole | |
| | TMP/SMX | |
| | Zafirlukast | |

*See Hansten,¹¹ Cupp and Tracy,¹² and Michalets.¹⁵

†NSAIDs indicates nonsteroidal anti-inflammatory drugs; TMP/SMX, trimethoprim-sulfamethoxazole.

cisapride, and muscle damage has occurred in patients taking lovastatin and simvastatin.^{17,18} Vincristine is associated with neurotoxic effects, while ergotamine is associated with ergotism (marked by cerebrosplinal symptoms, spasms, cramps, or a kind of dry gangrene). Various toxic effects have

occurred with carbamazepine, cyclosporine, disopyramide, protease inhibitors, rifabutin, tacrolimus, and triazolam.^{17,18} Cytochrome P450 activity varies from patient to patient, and these differences may increase the sensitivity to drug interactions involving CYP3A4 competition in pa-

tients with low CYP3A4 activity. More work in the area of interpatient variability is needed,¹¹ but it is likely that there are a number of parallels to the well-documented adverse effects that can occur when patients who lack the CYP2D6 isoform take many of the commonly prescribed psychotropic or cardiovascular drugs.

Adverse drug reactions, including drug-drug interactions, have important clinical implications for both physicians and patients. A recent survey found that the overall incidence of serious ADRs, including those that required hospitalization, those that were permanently disabling, and those that resulted in death was 6.7% of hospitalized patients.¹⁹ It has been estimated that in 1994, 106 000 patients had fatal ADRs, making these reactions between the fourth and sixth leading causes of death in the United States.¹⁷ Another recent survey found that, among hospitalized patients, the estimated per patient, postevent cost of a preventable ADR was \$4865, and the annual costs attributable to preventable ADRs for a 700-bed teaching hospital were \$2.8 million.²⁰

Lovastatin, simvastatin, atorvastatin, and cerivastatin are primarily metabolized by CYP3A4, although other pathways may play a minor role in the metabolic process.^{21,22} Fluvastatin is chiefly metabolized by CYP2C9 isoform, although modest metabolism by 3A4 and 2D6 also occurs.^{23,24}

In contrast, pravastatin does not undergo substantial metabolism by CYP450 isoenzymes. It modestly inhibits CYP3A4, 2C9, and 2D6, but is without specificity for any of these isoforms.²⁴ Because less than 1% of pravastatin is metabolized by CYP3A4, it exhibits no clinically significant alterations when administered with other agents that inhibit this isoform.²⁵

METABOLIC DIFFERENCES AMONG THE HMGs: CLINICAL DATA

There is a growing body of clinical data related to the metabolic differences among the HMGs and the clinical consequences of these differences. These findings are summarized in the following paragraphs.

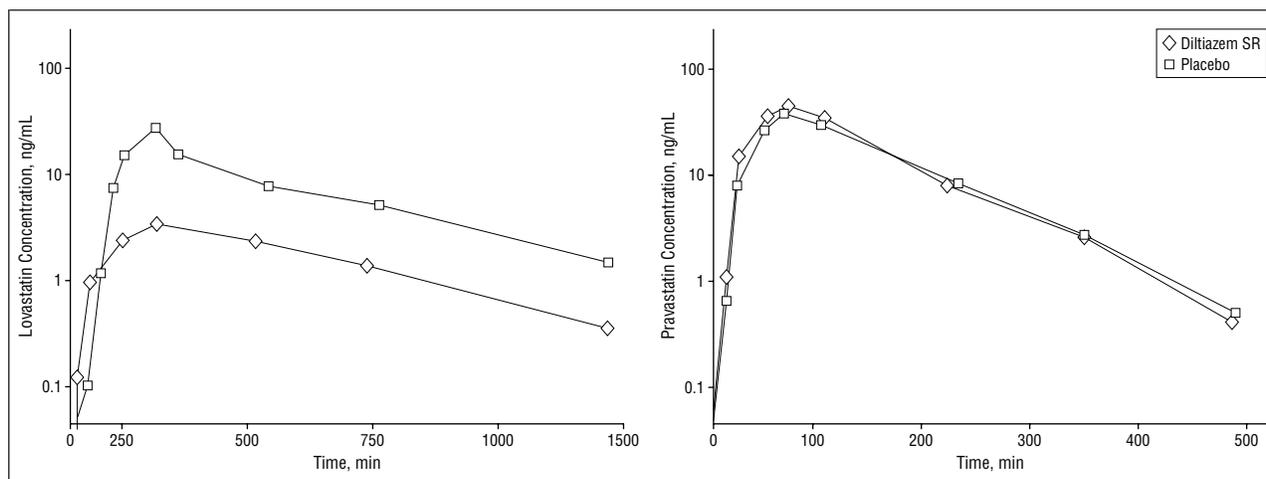


Figure 1. Effects of diltiazem on serum concentrations of lovastatin and pravastatin. Reprinted from Azie et al²⁶ with permission. SR indicates slow release.

Drug Interaction Studies

Drug interaction studies have provided a wealth of information about the metabolic differences among the various HMGs. The designs and results of 4 representative studies are described below.

In these studies, increases in the area under the curve (AUC) are particularly noteworthy. The term AUC refers to the concentration of drug in the systemic circulation during the dosing interval and is a reflection of the systemic exposure.²⁶ An increase in systemic exposure increases the likelihood that an adverse event will occur. For example, concomitant administration of terfenadine, a CYP3A4 substrate, with a 3A4 inhibitor such as erythromycin results in elevated plasma levels of terfenadine, which may lead to a clinically significant increase in mean rate-corrected QT interval duration and ventricular arrhythmias.¹⁰

Effects of Diltiazem on Lovastatin and Pravastatin. The effects of diltiazem, a moderate CYP3A4 inhibitor, on the pharmacokinetics of lovastatin and pravastatin were assessed in 10 healthy volunteers.²⁶ This randomized, open-label 4-way crossover study had a 2-week wash-out period between phases. The 4 study arms included administration of a single oral dose of (1) 20 mg of lovastatin after 2 weeks of placebo, (2) 20 mg of pravastatin after 2 weeks of placebo, (3) 20 mg of lovastatin after 2 weeks of treatment with 120 mg of slow-release diltia-

zem twice daily, and (4) 20 mg of pravastatin after 2 weeks of treatment with 120 mg of slow-release oral diltiazem twice daily.

Diltiazem significantly increased the peak concentration (C_{max}) of lovastatin from 6 ng/mL to 26.9 ng/mL ($P = .001$) and its AUC from 3607 ng/mL per minute to 12886 ng/mL per minute; the elimination half-life and time to C_{max} were not affected (**Figure 1**). As shown by the dramatic increase in AUC, systemic exposure to lovastatin was greatly increased. Diltiazem did not affect the AUC, C_{max} , half-life, or time to C_{max} of pravastatin. Diltiazem AUCs did not differ significantly between the lovastatin and pravastatin arms.

Effects of Itraconazole on Atorvastatin, Lovastatin, Simvastatin, and Pravastatin. In a randomized, crossover study, 10 healthy volunteers ingested 200 mg of itraconazole or placebo daily for 4 days.²⁷ On day 4, 40 mg of atorvastatin was administered, and itraconazole or placebo was administered 24 hours later. Itraconazole increased the AUC and half-life of atorvastatin acid 3-fold ($P < .001$), the AUC of atorvastatin lactone 4-fold ($P < .001$), and the C_{max} and half-life more than 2-fold ($P < .01$).

Twelve healthy volunteers were given 40 mg of lovastatin with placebo. After they were treated with itraconazole, a CYP3A4 inhibitor, at a dose of 200 mg/d for 4 days,²⁸ their AUCs of lovastatin and lovastatin acid increased 20-fold. There was a

10-fold increase in creatine kinase (CK) levels within 24 hours in one subject receiving concomitant lovastatin and itraconazole; this elevation did not occur when that person received lovastatin alone.

Two randomized, double-blind, 2-phase crossover studies were performed using an identical study design, one with 40 mg of simvastatin and the other with 40 mg of pravastatin.²⁹ In each study, 10 healthy young adults received either 200 mg of itraconazole or placebo orally once a day for 4 days. On day 4, each subject ingested a single 40-mg dose of simvastatin or pravastatin. Itraconazole increased the C_{max} and AUC of total simvastatin acid (simvastatin acid plus that derived by hydrolysis of the lactone) by 17-fold and the AUC by 19-fold ($P < .001$ for each) (**Figure 2**). The half-life was increased by 25% ($P < .05$). Itraconazole slightly increased the C_{max} and AUC of pravastatin, but the changes were not significant and the half-life was not altered.

These studies demonstrate that 3A4 inhibitors like diltiazem and itraconazole inhibit the CYP3A4-mediated metabolism of atorvastatin, lovastatin, and simvastatin, and their metabolites, increasing the serum concentrations and risk of skeletal muscle toxic effects. As we will discuss, similar increases in serum concentrations have caused serious adverse drug reactions in susceptible individuals. Pravastatin was not substantially affected by 3A4-mediated inhibition.

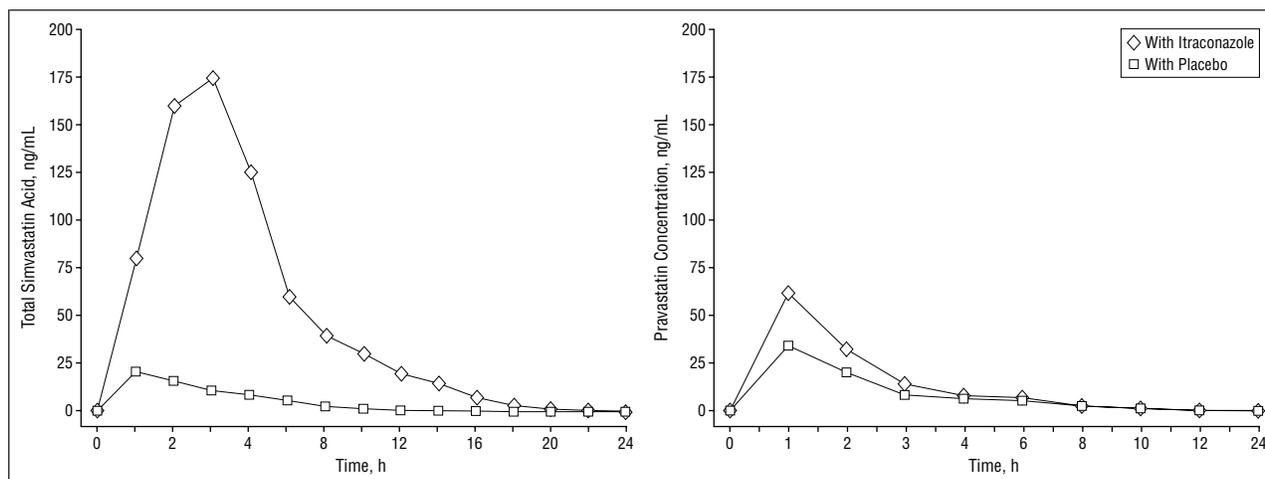


Figure 2. Effects of itraconazole on serum concentrations of simvastatin and pravastatin. Reprinted from Neuvonen et al²⁹ with permission.

Table 4. Serum HMG Drug Concentrations Reported After Clinically Significant Drug Interactions*

| Reference | HMG and Dose, mg | Cytochrome P Inhibitor | Serum Concentration† | ADR |
|-----------------------------|------------------|------------------------------|---|----------------------------|
| Spach et al ³⁰ | Lovastatin, 40 | Erythromycin | Lovastatin: 3 × increase | Rhabdomyolysis – died |
| Ayanian et al ³⁴ | Lovastatin, 60 | Erythromycin Diltiazem | Lovastatin: 8 × increase | Rhabdomyolysis – recovered |
| Segaert et al ⁴⁰ | Simvastatin, 40 | Itraconazole Cyclosporine | Simvastatin: 5.5 × increase Simvastatin acid: 13 × increase‡ | Rhabdomyolysis – recovered |
| Norman et al ⁴³ | Lovastatin, 80 | Cyclosporine | Lovastatin: 5 × increase | Rhabdomyolysis – recovered |

*HMG indicates hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors; ADR, adverse drug reaction.

†Fold increase from average serum concentration for dose.

‡Simvastatin acid: total of simvastatin acid form plus active simvastatin hydroxyacid (metabolite).

Clinical Implications of Drug Interaction Studies. These studies illustrate the importance of understanding the differences in the metabolism of the various HMGs and their potential for drug interactions. The results of these drug interaction studies emphasize the importance of (1) avoiding, whenever possible, the concomitant prescription of an HMG with an agent that can increase the systemic exposure of the HMG and (2) closely monitoring patients for potential drug interactions and subsequent ADRs when they are taking an HMG together with 1 or more agents that can precipitate a drug-drug interaction with that HMG.

Drug Interactions and Rhabdomyolysis

Clinically significant drug-drug interactions have resulted from inhibition of liver metabolism of lovastatin and simvastatin, and there is the potential for similar interactions with

atorvastatin and cerivastatin because they are also metabolized by CYP3A4. Drug interactions with the HMGs are a matter of concern because they can cause CK level elevations, myalgia, myopathy, and, extremely rarely, rhabdomyolysis.³⁰⁻³²

Rhabdomyolysis has been reported in patients receiving concomitant lovastatin and itraconazole,³³ erythromycin,^{34,35} cyclosporine,³⁶ and diltiazem.³⁷ It has also been reported when simvastatin was administered with cyclosporine,³⁸ nefazodone,³⁹ itraconazole,⁴⁰ and mibefradil.⁴¹ Atorvastatin plasma levels have increased when that HMG was administered with erythromycin⁴² and itraconazole,²⁷ although patients remained asymptomatic.

Clinically significant drug-drug interactions have also resulted from inhibition of liver metabolism by fluvastatin, which is metabolized and inhibits the CYP2C9.²³ Three patients receiving stable doses of the anticoagulant warfarin exhibited increased in-

ternational normalized ratios when fluvastatin was added to the regimen.²⁴ International normalized ratios are of clinical significance in establishing a therapeutic range for oral anticoagulation in patients at risk for thromboembolic events. There is also the potential for elevated plasma levels of phenytoin, tolbutamide, and diclofenac when these agents are given concomitantly with fluvastatin.

Pravastatin, unlike other HMGs, does not undergo extensive liver metabolism. Therefore, no clinically significant plasma elevations are expected to occur when it is administered with CYP450 inhibitors or substrates.

Valuable information has been gained by evaluating serum HMG drug concentrations in case reports of clinically significant drug interactions^{30,34,40,43} (Table 4). It is important to understand the relationship between the results of pharmacokinetic studies and clinical case reports of myopathy and rhabdo-

myolysis for which HMG drug concentrations are available. The CYP450 inhibitors in these case reports seem to elevate serum drug concentrations of the parent compound and the acid metabolite to a similar degree as in the drug interaction studies, suggesting that there is a pharmacokinetic basis for this interaction.

Case Reports of Myopathy or Rhabdomyolysis

There have been case reports of patients who developed myopathy or rhabdomyolysis while receiving concomitant therapy with either lovastatin and simvastatin and 1 or more CYP3A4 inhibitors. Despite their infrequency, these reports provide insight into implications for long-term safety of HMGs.

Rhabdomyolysis With Lovastatin and Erythromycin. This case was reported as a drug-drug interaction in 1991.³⁰ The patient was a 68-year-old woman with coronary artery disease, diabetes mellitus, congestive heart failure, chronic renal failure, and hypercholesterolemia. Her medication included furosemide, succalfate, ranitidine, allopurinol, insulin, nitrates, enalapril, digoxin, and 20 mg of lovastatin twice daily. At the time of the interaction, she had just completed a 10-day course of treatment with erythromycin for pneumonia, and her pulmonary and cardiac function were normal.

Five days after completing the erythromycin treatment, the patient complained of muscle weakness and tenderness. Within 24 hours of the onset of myalgias, she exhibited signs of rhabdomyolysis. Her urine became dark; CK level was 26 400 U/L; urine output was 10 mL/h; and her serum creatinine level was 309.4 to 371.3 $\mu\text{mol/L}$ (3.5-4.2 mg/dL). A lovastatin serum concentration level at this time was 48 ng/mL, or only 3 times the normal level. The patient refused to undergo renal dialysis and died 2 days later of progressive renal failure and pulmonary edema.

This case illustrates that even with short-term use, potent inhibitors of CYP3A4 such as erythromycin may produce myopathy and rhabdomyolysis during a short

course (<2 wk) of coadministration with lovastatin. In addition, this fatal reaction occurred with serum concentrations only 3 times normal levels. Serum concentrations in this range are easily obtainable with CYP3A4 inhibition as demonstrated in several pharmacokinetic studies.²⁶⁻²⁹ Because HMG therapy is given on a long-term basis, a patient may be at risk of a drug-drug interaction several times during the treatment course because of the concomitant use of numerous commonly prescribed drugs such as antibiotics and calcium channel blockers. It is important for physicians to recognize these potential interactions and to avoid these combinations if possible.

Myopathy With Lovastatin and Diltiazem. This case was reported as an ADR in 1993.³⁷ The patient was a 53-year-old man with hypertension, coronary artery disease, and hypercholesterolemia. He was receiving a typical regimen of nitrates, diltiazem, enalapril, and lovastatin.

Following several months of treatment with these drugs, the patient began to experience signs and symptoms of myopathy. He complained of pain in both upper and lower extremities so severe that it impeded his ability to walk. Results of an electromyogram revealed a myopathic pattern, and the CK level was 4000 U/L.

One week after discontinuation of both lovastatin and diltiazem therapy, the patient's myopathy improved. Lovastatin treatment was resumed shortly thereafter with no further signs or symptoms of myopathy. However, when diltiazem was added to the regimen, very high creatine phosphokinase levels and myopathy again developed. Based on the rationale that the patient's myopathy did not occur until diltiazem was added to the regimen, the author³⁷ concluded that diltiazem was responsible for the myopathy.

The author's attribution of causation is noteworthy because it illustrates the widespread tendency to identify the last agent added to the regimen as the offending agent. In this case, however, the patient's myopathy was most likely due to an elevation in lovastatin concentra-

tions caused by the inhibition of lovastatin metabolism by diltiazem. In this situation, diltiazem treatment would likely be discontinued and lovastatin continued. However, the adverse reaction could recur if another CYP3A4 inhibitor was later added.

To avoid further complications, lovastatin could be replaced with another HMG less likely to undergo CYP450 inhibition. Following that substitution, diltiazem or other CYP450 inhibitors could be continued without increased risk of adverse reactions. Although diltiazem is usually considered a modest inhibitor of CYP3A4 activity, as this case suggests, some patients may experience myopathy with commonly administered inhibitors like some calcium channel blockers.

Rhabdomyolysis With Simvastatin and Itraconazole. This case was reported as rhabdomyolysis in 1996.⁴⁴ A 74-year-old man with hypertension and hyperlipidemia was stabilized on a regimen of lisinopril, aspirin, and 40 mg/d of simvastatin. His health was otherwise excellent. On presentation for treatment of fungal toenails, itraconazole was prescribed following confirmation of dermatophytic infection and receipt of a normal baseline multichemistry profile and urinalysis.

After 3 weeks, the patient developed leg pain and then arm and neck pain. He discontinued itraconazole, simvastatin, and lisinopril treatment, suspecting an adverse drug reaction. His urine became brown. At presentation, his CK level was found to be 22.8×10^6 U/L, and his lactic dehydrogenase value was 927 000 U/L. The patient was advised to drink large quantities of water and to limit his physical activities. Laboratory values began to return to normal after 36 hours.

Myositis and Rhabdomyolysis With Simvastatin and Nefazodone. This case was reported as myositis and rhabdomyolysis in 1997.³⁹ The patient was a 44-year-old man who had been asymptomatic while taking 40 mg/d of simvastatin for 19 weeks. At that point, he began treatment with 200 mg/d of nefazodone for depression.

One month later, when the patient complained of dark urine, he was treated with amoxicillin and clavulanate potassium for a presumed urinary tract infection. When he returned for a follow-up examination after 2 months of concomitant therapy with simvastatin and nefazodone, he again complained of dark urine and also of severe myalgias. His CK level was 6081 U/L.

Both simvastatin and nefazodone treatment were immediately discontinued and oral hydration with alkalinized fluids was begun. Within 3 weeks, the patient was asymptomatic, and laboratory values had returned to normal.

The authors³⁹ speculated that the introduction into the regimen of nefazodone, a CYP3A4 inhibitor, inhibited the metabolism of simvastatin to the point that it caused a dramatic increase in the serum concentration of simvastatin and then rhabdomyolysis. They suggested that nefazodone be avoided in patients taking simvastatin or other drugs metabolized by CYP3A. Avoidance of the combination of simvastatin and nefazodone or earlier detection of the interaction by the patient's physician or pharmacist might have prevented the unnecessary use of antibiotics and limited the severity of the interaction.

Rhabdomyolysis With Simvastatin and Mibefradil. After receiving 7 reports of rhabdomyolysis in patients taking simvastatin and mibefradil concomitantly, the US Food and Drug Administration (FDA) issued a warning label in December 1997.⁴¹ This label contraindicated the coadministration of mibefradil with either lovastatin or simvastatin because both of these HMGs are dependent on CYP3A4 for their metabolism. The FDA also warned against the coadministration of mibefradil with either atorvastatin or cerivastatin pending further investigation. The case reports received by the FDA illustrate the potential harm that can occur when the serum concentrations of HMGs are elevated by CYP3A4 inhibition. In contrast, the FDA has stated that since pravastatin and fluvastatin are not metabolized by CYP3A4, mibefradil would not be expected to have

significant effects on their blood levels or to increase the risk of muscle injury.

Following 19 reported cases of rhabdomyolysis when given concomitantly with simvastatin, including at least one death, mibefradil was voluntarily removed from the market in June 1998 because of a high potential for causing drug interactions.⁴⁵

Rhabdomyolysis With Pravastatin. Rare cases of rhabdomyolysis have been reported with pravastatin.^{46,47} However, no cases have been reported with concomitant medications that inhibit the CYP3A4 isoform.

CLINICAL IMPLICATIONS OF DRUG METABOLISM DURING HMG THERAPY: GUIDELINES FOR HMG THERAPY

Drug-drug interactions between lovastatin, simvastatin, atorvastatin, or cerivastatin and a CYP3A4 inhibitor such as diltiazem, verapamil, erythromycin, or clarithromycin may lead to increased plasma concentrations of the HMG. When used as monotherapy, the HMGs have rarely been associated with the development of ADRs ranging from myalgia and myositis to rhabdomyolysis. Data suggest that myotoxic effects may be most likely to occur with lipophilic agents such as lovastatin and simvastatin and in patients with renal dysfunction.^{48,49} Rhabdomyolysis has also occurred due to interactions between lovastatin and simvastatin and concomitantly administered agents that inhibit the CYP3A4 system. Therefore, the potential for clinically significant drug interactions must be considered when selecting an HMG for high-risk patients.

Because pravastatin is not substantially metabolized by the CYP3A4, pravastatin plasma concentrations would not be expected to increase in the presence of other CYP3A4 inhibitors. Coadministration of diltiazem, erythromycin, or itraconazole has not resulted in significant increases in pravastatin serum concentrations.⁵

In considering the choice of an HMG for a particular patient, the

physician must remember that many factors influence the outcome of drug interactions in the clinical setting. There is marked variability from patient to patient and from drug to drug, which makes it very difficult to determine who is most susceptible to adverse effects.¹¹ Some patient factors include genetic makeup, the presence of intercurrent disease, dietary/nutritional factors, environmental factors, smoking, and alcohol consumption. Variations in drug factors include the ways that potentially interacting drugs are administered (including dose, duration, dosing times, sequence of administration, route, and dosage form).

When considering the selection of an HMG, the physician must review the most recent clinical outcome data and determine the potential for drug interactions in each patient. Because of the lack of clinically significant drug interactions, pravastatin can be given safely to patients taking medication metabolized by the CYP3A4 isoform, to patients who are taking multiple medications (such as patients with heart disease), and to organ transplant recipients.

CONCLUSIONS

Pharmacokinetic properties vary among the HMGs. In terms of long-term safety, the most important distinction is the varying metabolic profiles of these agents. Lovastatin, simvastatin, atorvastatin, and cerivastatin are chiefly metabolized by CYP3A4, whereas fluvastatin is primarily metabolized by CYP2C9. Pravastatin is not metabolized to a significant extent by the CYP450 system. Because of these metabolic differences, the potential for drug interactions differs among the various HMGs.

Physicians must take many factors into consideration when choosing which member of a therapeutic class to prescribe for a patient. One factor that should be kept in mind is that the inhibition of CYP3A4 may produce severe toxic effects. As with other drug therapy decisions, the potential for clinically significant drug interactions must be considered when selecting an HMG for long-term therapy.

REFERENCES

1. Lennernas H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet*. 1997;32:403-425.
2. White CM, Chow MSS. A review of HMG-CoA reductase inhibitors. *US Pharmacist*. January 1998; HS19-HS30.
3. Mevacor. In: *Physicians' Desk Reference*. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998: 1694-1698.
4. Zocor. In: *Physicians' Desk Reference*. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998: 1776-1780.
5. Pravachol. In: *Physicians' Desk Reference*. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998: 808-811.
6. Lescol. In: *Physicians' Desk Reference*. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998: 1862-1865.
7. Lipitor. In: *Physicians' Desk Reference*. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998: 2186-2189.
8. Baycol. In: *Physicians' Desk Reference*. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998: 603-606.
9. Hamelin B, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol Sci*. 1998;19:26-37.
10. Seldane. In: *Physicians' Desk Reference*. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998: 1238-1244.
11. Hansten PD. Understanding drug-drug interactions. *Sci Med*. January/February 1998:16-25.
12. Cupp MJ, Tracy TS. Cytochrome P450: new nomenclature and clinical implications. *Am Fam Physician*. 1998;57:107-116.
13. Benet LZ, Kroetz DL, Sheiner LB. Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 9th ed. New York, NY: McGraw-Hill Co; 1996:12-17.
14. Horsmans Y. Major cytochrome P-450 families: implications in health and liver diseases. *Acta Gastroenter Belg*. 1997;60:2-10.
15. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy*. 1998;18:84-112.
16. Levy RH, Bajpai M. Phenytoin: interactions with other drugs—mechanistic aspects. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 4th ed. New York, NY: Raven Press; 1995:329-338.
17. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998; 279:1200-1205.
18. Bates DW, Spell N, Cullen DJ, et al, for the Adverse Drug Events Prevention Study Group. The costs of adverse drug events in hospitalized patients. *JAMA*. 1997;277:307-311.
19. Hansten PD, Horn JR. *Drug Interactions Analysis and Management*. Vancouver, Wash: Applied Therapeutics; 1998.
20. Ruzack MA. *The Medical Letter Handbook of Adverse Drug Interactions*. New Rochelle, NY: The Medical Letter; 1997.
21. Desager JP, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet*. 1996; 31:348-371.
22. Boberg M, Angerbauer R, Fey P, et al. Metabolism of cerivastatin by human liver microsomes in vitro. Characterization of primary metabolic pathways and of cytochrome P450 enzymes involved. *Drug Metab Dispos*. 1997;25:321-331.
23. Transon C, Leemann T, Vogt N, Dayer P. In vivo inhibition profile of cytochrome P450TB (CYP2C9) by \pm fluvastatin. *Clin Pharmacol Ther*. 1995;58: 412-417.
24. Trilli LE, Kelley CL, Aspinall SL, Kroner BA. Potential interaction between warfarin and fluvastatin. *Ann Pharmacother*. 1996;30:1399-1402.
25. Everett DW, Chando TJ, Didonato GC, Singhvi SM, Pan HY, Weinstein SH. Biotransformation of pravastatin sodium in humans. *Drug Metab Dispos*. 1991;19:740-748.
26. Azie NE, Brater DC, Becker PA, Jones DR, Hall SD. Interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther*. 1998;64:369-377.
27. Kantola T, Kivist KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther*. 1998;64:58-65.
28. Neuvonen PJ, Jalava KM. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther*. 1996;60:54-61.
29. Neuvonen PJ, Kantola T, Kivist KT. Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther*. 1998;63:332-341.
30. Spach DH, Bauwens JE, Clark CD, Burke WG. Rhabdomyolysis associated with lovastatin and erythromycin use. *West J Med*. 1991;154:213-215.
31. Rosenberg AD, Neuwirth MG, Kagen LJ, Singh K, Fischer HD, Bernstein RL. Intraoperative rhabdomyolysis in a patient receiving pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor. *Anesth Analg*. 1995;81:1089-1091.
32. Veerkamp JH, Smit JW, Benders AA, Oosterhof A. Effects of HMG-CoA reductase inhibitors on growth and differentiation of cultured rat skeletal muscle cells. *Biochim Biophys Acta*. 1996;1315: 217-222.
33. Lees RS, Lees AM. Rhabdomyolysis from the coadministration of lovastatin and the antifungal agent itraconazole. *N Engl J Med*. 1995;333:664-665.
34. Ayanian JZ, Fuchs CS, Stone RM. Lovastatin and rhabdomyolysis. *Ann Intern Med*. 1988;115:682-683.
35. Ballantyne CM, Radovancevic B, Farmer JA, et al. Hyperlipidemia after heart transplantation: report of a 6-year experience, with treatment recommendations. *J Am Coll Cardiol*. 1992;19:1315-1321.
36. Corpier CL, Jones PH, Suki WN, et al. Rhabdomyolysis and renal injury with lovastatin use. *JAMA*. 1988;260:239-241.
37. Ahmad S. Diltiazem myopathy. *Am Heart J*. 1993; 126:1494-1495.
38. Meier C, Stey C, Brack T, Maggiorini M, Risti B, Krahenbuhl S. Rhabdomyolysis in patients treated with simvastatin/cyclosporine: role of the hepatic cytochrome P450 enzyme. *Schweiz Med Wochenschr*. 1995;125:1342-1346.
39. Jacobson RH, Wang P, Glueck CJ. Myositis and rhabdomyolysis associated with current use of simvastatin and nefazodone [letter]. *JAMA*. 1997; 277:296.
40. Segaert MF, De Soete C, Vandewiele I, Verbanck J. Drug-interaction-induced rhabdomyolysis. *Nephrol Dial Transplant*. 1996;11:1846-1847.
41. US Food and Drug Administration. *Posicor Labeling Changes*. Washington, DC: US Food and Drug Administration; December 18, 1997. Talk Paper No. not available.
42. Yang B-B, Siedlik PH, Smithers JA, Sedman AJ, Stern RH. Atorvastatin pharmacokinetic interactions with other CYP3A4 substrates: erythromycin and ethinyl estradiol [abstract]. *Pharm Res*. 1996;13(suppl 9):S437.
43. Norman DJ, Illingworth DR, Munson J, Hosenpud J. Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. *N Engl J Med*. 1988;318:46-47.
44. Horn M. Coadministration of itraconazole with hypolipidemic agents may induce rhabdomyolysis in healthy individuals. *Arch Dermatol*. 1996;132:1254.
45. Schmassmann-Suhijar D, Bullingham R, Gasser R, Schmutz J, Haefeli WE. Rhabdomyolysis due to interaction of simvastatin with mibefradil. *Lancet*. 1998;351:1929-1930.
46. Decoux E, Millaire A, De Groote P, Mahieux G, Ducloux G. Rhabdomyolysis with pravastatin and type I macrocreatine kinase. *Ann Cardiol Angiol*. 1993;42:267-269.
47. Ragazzi MB, Iacona I, Campana C, et al. Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc*. 1993;25:2732-2734.
48. Perault MC, Ladouch-Bures L, Dejean C, Delaunay C, Pouget Abadie JF, Vandel B. Rhabdomyolysis during pravastatin treatment. *Therapie*. 1993;48:487.
49. Biesenbach G, Janko O, Stuby U, Zazgornik J. Myoglobinuric renal failure due to long-standing lovastatin therapy in a patient with pre-existing chronic renal insufficiency. *Nephrol Dial Transplant*. 1996;11:2059-2060.