THE 3-HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE INHIBITOR
FLUVASTATIN: EFFECT ON HUMAN CYTOCHROME P-450 AND IMPLICATIONS FOR
METABOLIC DRUG INTERACTIONS

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ABSTRACT:
Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, was metabolized by human liver microsomes to 5-hydroxy-, 6-hydroxy-, and N-deisopropyl-fluvastatin. Total metabolite formation was biphasic with apparent Kₘ values of 0.2 to 0.7 and 7.9 to 50 μM and intrinsic metabolic clearance rates of 1.4 to 4 and 0.3 to 1.5 ml/h/mg microsomal protein for the high and low Kₘ components, respectively. Several enzymes, but mainly CYP2C9, catalyzed fluvastatin metabolism. Only CYP2C9 inhibitors such as sulfaphenazole inhibited the formation of both 6-hydroxy- and N-deisopropyl-fluvastatin. 5-Hydroxy-fluvastatin formation was reduced by compounds that are inhibitors of CYP2C9, CYP3A4, or CYP2C8. Fluvastatin in turn inhibited CYP2C9-catalyzed tolbutamide and diclofenac hydroxylation with Kᵢ values of 0.3 and 0.5 μM, respectively. For CYP2C8-catalyzed 6α-hydroxy-paclitaxel formation the IC₅₀ was 20 μM and for CYP1A2, CYP2C19, and CYP3A catalyzed reactions, no IC₅₀ could be determined up to 100 μM fluvastatin. All three fluvastatin metabolites were also formed by recombinant CYP2C9, whereas CYP1A1, CYP2C8, CYP2D6, and CYP3A4 produced only 5-hydroxy-fluvastatin. Kₘ values were ~1, 2.8, and 7.1 μM for CYP2C9, CYP2C8, and CYP3A, respectively. No difference in fluvastatin metabolism was found between the CYP2C9R144 and CYP2C9 C144 alleles, suggesting the absence of polymorphic fluvastatin metabolism by these alleles. CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2E1, and CYP3A5 did not produce detectable amounts of any metabolite. This data indicates that several human cytochrome P-450 enzymes metabolize fluvastatin with CYP2C9 contributing 50-80%. Any coadministered drug would therefore only partially reduce the metabolic clearance of fluvastatin; therefore, the likelihood for serious metabolic drug interactions is expected to be minimal.

Fluvastatin (Lescol) is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)₁ reductase inhibitor which consistently lowers low density lipoprotein cholesterol levels by 20 to 30% at a daily dose of 20 to 40 mg (Levy et al., 1993; Peters et al., 1993; Davidson, 1994). Like most HMG-CoA reductase inhibitors, fluvastatin has a low incidence rate (<0.5%) of musculoskeletal side effects such as myopathy and rhabdomyolysis. These side effects, however, increase for certain HMG-CoA reductase inhibitors with increased systemic concentrations of the HMG-CoA reductase inhibitors when coadministered with other drugs. Lovastatin plasma exposure (area under the plasma concentration time curve), for example, increases 20-fold when coadministered with cyclosporine A (Olbright et al., 1997) and the incidence of musculoskeletal side effects increases up to 28% (Tober, 1988). In combination with itraconazole, lovastatin concentrations increase 10-fold (Kantola et al., 1997); this combination has been associated with rhabdomyolysis (Lees and Lees, 1995). Most of these interactions have been attributed to the inhibition of CYP3A, which is the major enzyme metabolizing most HMG-CoA reductase inhibitors including lovastatin, simvastatin, atorvastatin, and cerivastatin (Wang et al., 1991; Pruksaritamont et al., 1997; Boberg et al., 1997; Physicians’ Desk Reference, 1998). Additional factors besides metabolism may also contribute to the observed drug interactions. For example, lovastatin has recently been shown to be a substrate for P-glycoprotein (Dimitroulakos and Yeger, 1996) and increased lovastatin concentrations could in part be due to a decrease of biliary clearance after P-glycoprotein inhibition. A similar mechanism might also explain increased (5–23-fold) plasma concentrations of pravastatin in the presence of cyclosporine A (Regazzi et al., 1993), because pravastatin is thought not to be metabolized by CYP3A.

For fluvastatin, relatively few cases of musculoskeletal side effects have been reported, even when administered in combination with other drugs (Peters et al., 1993; Peters, 1996; Plosker and Wagstaff, 1996). This may be attributed to its favorable biopharmaceutical profile. Fluvastatin is completely absorbed from the intestinal tract. Systemic exposure, however, is limited due to first-pass metabolism with maximal plasma concentrations of 0.35 μM after a 40-mg (0.1-mMol) oral dose. Fluvastatin is almost exclusively eliminated via metabolism, mainly hydroxylation, at the 5- and 6-position of the indole moiety and N-deisopropylation. Only the hydroxylated metabolites retain some HMG-CoA reductase inhibitory activity, yet they...
are not found in the systemic circulation (Tse et al., 1992; Dain et al., 1993).

Based on these pharmacokinetic characteristics, transport proteins such as P-glycoprotein should not be involved in the disposition of fluvastatin. Drug interactions affecting fluvastatin disposition should therefore be limited to metabolic interactions. However, although fluvastatin has been reported to inhibit CYP3A competitively at high (200 μM) concentrations (Ikeda et al., 1997), CYP3A does not appear to be the major enzyme eliminating fluvastatin. CYP3A inhibitors do not affect fluvastatin to the same extent as the other HMG-CoA reductase inhibitors. Fluvastatin area under the plasma concentration time curve has been increased only 1.9-fold in the presence of cyclosporine A (Goldberg and Roth, 1996) and fluvastatin plasma concentrations have been unchanged when given together with itraconazole (Kantola et al., 1997). At much lower concentrations (~0.2 μM), fluvastatin has been reported to also competitively inhibit CYP2C9 (Transon et al., 1996).

The objective of this study was to further define the enzymes involved in fluvastatin elimination using in vitro techniques. Furthermore, the reciprocal effects on the biotransformation of fluvastatin and potentially coadministered drugs were assessed to provide guidance for clinical use.

Materials and Methods

Chemicals. [14C]Fluvastatin (2 GBq/mmol) (R*, S*-(+) -7-[3-(4-fluorophenyl)-(1-methyl)ethyl]-3,5-dihydroxy-6-heptenoic acid monosodium salt) was obtained from Novartis Pharmaceuticals Corporation (East Hanover, NJ). The purity of the labeled fluvastatin was 94.5% by HPLC. [3H]Glibenclamide (1.35 GBq/mmol, cyclohexol-3,3-[3H]) was obtained from DuPont-NEN (Boston, MA). [14C]Pralnitazone (2.3 GBq/mmol, 2-benzyl ring)-[14C]Phenacetin (0.5 GBq/mmol, phenacetin-ring-[14C]) were obtained from Sigma (St. Louis, MO). [14C]Tobutamidine (2 GBq/mmol), [14C]-N-methylphenyl (2.2 GBq/mmol), and [14C]cyclopine A (296 GBq/mmol) were obtained from Amersham (Little Chalfont, UK).

Unlabeled diclofenac, 4′-hydroxy-diclofenac, valsartan, cyclosporine A, isradipine, and fluvastatin metabolites (5-hydroxy-, 6-hydroxy- and N-desisopropyl-fluvastatin) were obtained from Novartis. Janssen Biotech NV (Olen, Belgium) provided itraconazole. Furafylline and ketoconazole were purchased from Ultrafine Chemicals (Manchester, UK). Chlorozoxazone, chlorpropane, sulfaphenazole, quinidine, erythromycin, sulfisoxazole, ethinyl estradiol, gliburide, troleandomycin, nifedipine, dextromethorphan, phenacetin, clofibrate, paclitaxel, sparteine, and tolbutamide were purchased from Sigma. Glibornuride and mibefradil were a gift from Hoffman-La Roche (Basel, Switzerland), lovastatin was obtained from Merck (West Point, PA), and pravastatin from Bristol-Myers Squibb (Princeton, NJ). All other reagents were obtained from commercial sources and were of the highest quality available.

Biologicals. Human liver tissue which could not be used for transplantation was obtained as either pieces or microsomes from the International Institute for the Advancement of Medicine (Exton, PA), GMM-002, from Vitron Inc, (Tucson, AZ). Liver tissue was separated from the denatured protein by centrifugal. The supernatant were directly analyzed by HPLC on either a HP1090 (Hewlett Packard, Waldbronn, Germany) or an Alliance (Waters, Milford, MA) system. Fluvastatin and its metabolites were separated by gradient HPLC (LC 18-DB, 5-μm particle size, 20 x 4.6 mm and 250 x 4.6 mm; Supelco Inc., Bellefonte, PA) with 10 mm ammonium acetate (pH 7.4) and methanol at a total flow of 1 ml/min at 50°C. Methanol was held constant at 0% for 3 min and then increased linearly to reach 35% at 33 min and then to 100% at 80 min. Glibornuride was chromatographed at 40°C (LC 18, 5-μm particle size, 20 x 2.1 mm and 100 x 2.1 mm; Brownlee, San Jose, CA) at a total flow of 0.4 ml/min. The mobile phases were 10 mm ammonium acetate (pH 4.3) and acetoni trile. The proportion of acetoni trile was increased linearly from 0 to 60% during 60 min. Acetonitrile reached 80% at 45 min and was held constant until 50 min. Mephenytoin was chromatographed at 25°C (C18 Genesis, 4 μm, 250 x 3.1 mm; Jones Chromatography Inc., Lakewood, CO). The mobile phases were 20 mm ammonium acetate (pH 7.4) and acetoni trile with a total flow rate of 0.6 ml/min. The proportion of acetoni trile was increased linearly from 0 to 100% during 30 min. Diclofenac was chromatographed at 40°C (LC 18-DB, 5-μm particle size, 30 x 4.6 mm and 250 x 4.6 mm) at a total flow of 1 ml/min. The mobile phase consisted of 100 mM sodium phosphate (80%) and acetoni trile (20%) containing triethylamine (0.02%). Fluvastatin, gliburide, and their metabolites were detected by radioactivity monitoring using β-Raman (IN/US Systems Inc., Tampa, FL) and glibornuride and alternatively gliburide by UV detection at 230 and 238 nm, respectively. Diclofenac and its 4′-hydroxy-metabolite were monitored by electrochemical detection using a Coullochem II (ESA Inc., Bedford, MA). All other compounds were analyzed essentially as described by Fischer et al. (1998). All compounds and metabolites were identified by their HPLC retention times and compared to chromatograms of reference compounds. Fluvastatin metabolites were additionally identified by liquid chromatography/mass spectrometry (LC/MS) analysis.

Mass Spectrometric Analysis. Liquid chromatography flow was split equally between the TSQ-7000 mass spectrometer (Finnigan MAT, San Jose, CA) and an INUS radioactivity monitor. Single and tandem quadrupole experiments were performed in the negative ion mode with an electrospray interface. Capillary temperature was 225°C and gas pressures were set at four bars for nitrogen sheath gas and one bar for nitrogen auxiliary gas. For most experiments, the electron multiplier setting was 1600 V. For tandem MS experiments, the collision cell voltage was 25 eV and the argon cell pressure was 1.3 x 10^-6 bar.

Data Analysis. Metabolic rates were calculated from mean substrate concentrations over the incubation period. IC50 values were determined graphically by plotting the percent of the control activity against the inhibitor concentration. Michaelis-Menten parameters Km and Vmax were determined by analysis of linearized plots as well as nonlinear curve fitting using Hyper.exe
Results

Biotransformation Pathways. Fluvastatin was metabolized in five different human liver microsomal preparations to three primary metabolites (Figs. 1A and 2). The metabolites exhibiting retention times of 42 and 45 min were identified as 6-hydroxy- and 5-hydroxy-fluvastatin, respectively, and the metabolite eluting at 52 min was identified as N-deisopropyl-fluvastatin. The assignment of the metabolite structures was based on LC/MS analysis and on retention times compared with synthetic reference compounds. The LC/MS analysis indicated changes of the nominal mass compared to fluvastatin of $M_1 = 16$ for 5-hydroxy- and 6-hydroxy-fluvastatin and of $M_2 = 42$ for N-deisopropyl fluvastatin. Quantitatively, at 0.2 to 0.6 $\mu$M fluvastatin concentrations in human liver microsomes, 5-hydroxy-fluvastatin was the most abundant metabolite, followed by 6-hydroxy-fluvastatin and N-deisopropyl-fluvastatin, which were of similar importance. Among the five livers studied, 5-hydroxy-fluvastatin formation varied 2- to 29-fold compared to 6-hydroxy-fluvastatin (data not shown), whereas there was less variability between 6-hydroxy-fluvastatin and N-deisopropyl-fluvastatin formation (0.7–1.4-fold).

Individual human P-450 isoenzymes expressed in human lymphoblast cells or in insect cells also metabolized fluvastatin, but only CYP2C9 formed all three metabolites produced by human liver microsomes (Fig. 1B). Recombinant human CYP3A4 (Fig. 1C), CYP2C8, CYP2D6, and CYP1A1 (data not shown) formed only 5-hydroxy-fluvastatin. Quantitatively, for CYP2C9, 6-hydroxy-fluvastatin is the most abundant metabolite, followed by 5-hydroxy-fluvastatin and N-deisopropyl-fluvastatin. There was no difference in fluvastatin metabolite formation between the CYP2C9 R144 allele and the CYP2C9 C144 allele. In contrast, CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2E1, and CYP3A5 did not produce detectable amounts of metabolites (data not shown).

Intrinsic Metabolic Clearance. The rate of fluvastatin metabolism was determined for three human liver microsomal preparations over a concentration range of 0.04 to 20 $\mu$M (Table 1) and for recombinant CYP2C8, CYP2C9, and CYP3A4 preparations (Table 2). In human liver microsomal preparations, metabolism appeared biphasic. For the lower substrate concentration (0.04–0.6 $\mu$M), the $K_m$ was similar for...
The largest effects were on the CYP2C9-catalyzed 6-hydroxy- and 6-deisopropyl-fluvastatin formation. Typical CYP3A-specific inhibitors such as ketoconazole and troleandomycin were only inhibitory for 5-hydroxy-fluvastatin formation, which is in part formed by CYP3A. Compounds such as phenacetin and furafylline did not affect metabolism of fluvastatin. Both are known to inhibit CYP1A2. Similarly, substrates of CYP2D6 (quinidine, dextromethorphan, and sparteine) or CYP2E1 (chloroxazone) had no relevant effect on fluvastatin metabolism.

Among the antihypertensive agents that might potentially be coadministered with fluvastatin, both nifedipine and isradipine were also inhibitory. The immunosuppressant cyclosporine A had only small inhibitory effect. The antihypercholesterolemic agents, lovastatin and clofibrate, inhibited both the 5-hydroxy-fluvastatin and N-deisopropyl-fluvastatin formation. Itraconazole of the metabolites, i.e., 5-hydroxy-fluvastatin formation. Itraconazole and terbinafine had little or no effect on any metabolite. The antihypertensive agents that might potentially be coadministered with fluvastatin, both nifedipine and isradipine were also inhibitory. The immunosuppressant cyclosporine A had only small inhibitory effect. The antihypercholesterolemic agents, lovastatin and clofibrate, inhibited both the 5-hydroxy-fluvastatin and N-deisopropyl-fluvastatin formation. Itraconazole and terbinafine had little or no effect on any metabolite. The antihypercholesterolemic agents, lovastatin and clofibrate, inhibited both the 5-hydroxy-fluvastatin and N-deisopropyl-fluvastatin formation. Itraconazole and terbinafine had little or no effect on any metabolite.

**Effect of Fluvastatin on the Metabolism of Other Drugs.** Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9 (Table 4). Fluvastatin was found to inhibit the metabolism of the CYP2C9 substrates diclofenac and tolbutamide.

<table>
<thead>
<tr>
<th>Human Liver</th>
<th>Metabolites</th>
<th>$K_{m}$</th>
<th>$V_{max}$</th>
<th>$V_{max}$</th>
<th>$Cl_{m}$</th>
<th>$Cl_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGM-002</td>
<td>All</td>
<td>0.7</td>
<td>30</td>
<td>2.6</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>6-OH + N-deisopropyl</td>
<td>0.2</td>
<td>0.3</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M8</td>
<td>All</td>
<td>0.5</td>
<td>35</td>
<td>1.9</td>
<td>50</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>6-OH + N-deisopropyl</td>
<td>0.3</td>
<td>0.6</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL45</td>
<td>All</td>
<td>0.2</td>
<td>24</td>
<td>0.3</td>
<td>7.9</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>6-OH + N-deisopropyl</td>
<td>0.1</td>
<td>0.1</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2

**Individual enzyme kinetic parameters for fluvastatin metabolism**

Michaels-Menten parameters were determined from recombinant baculovirus/insect cell microsomes expressing active, human CYP2C8, CYP2C9<sub>R144</sub>, CYP2C9<sub>C144</sub> or CYP3A4. Maximal velocities were extrapolated to human liver microsomes using the ratio of reference activities in a panel of human liver microsomes compared recombinant with enzymes: CYP3A, testosterone; CYP2C9, diclofenac; CYP2C8 6a-hydroxy-paclitaxel (Crespi and Penman, 1997).

<table>
<thead>
<tr>
<th>Recombinant Enzymes</th>
<th>CYP (nmol/h/mg protein)</th>
<th>CYP (nmol/h/mg protein)</th>
<th>CYP (ml/h/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 3A4/5-OH*</td>
<td>7.1</td>
<td>120 (29)</td>
<td>14 (5.7)</td>
</tr>
<tr>
<td>CYP 2C9&lt;sub&gt;R144&lt;/sub&gt;/6-OH</td>
<td>0.9</td>
<td>4.7 (2.4)</td>
<td>1.1 (0.5)</td>
</tr>
<tr>
<td>CYP 2C9&lt;sub&gt;R144&lt;/sub&gt;/5-OH</td>
<td>1.0</td>
<td>2.3 (1.2)</td>
<td>0.5 (0.2)</td>
</tr>
<tr>
<td>CYP 2C9&lt;sub&gt;R144&lt;/sub&gt;/N-deisopropyl</td>
<td>1.8</td>
<td>2.3 (1.2)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>CYP 2C9&lt;sub&gt;C144&lt;/sub&gt;/6-OH</td>
<td>1.2</td>
<td>3.6 (1.7)</td>
<td>1.1 (0.5)</td>
</tr>
<tr>
<td>CYP 2C9&lt;sub&gt;C144&lt;/sub&gt;/5-OH</td>
<td>1.0</td>
<td>1.5 (0.7)</td>
<td>0.5 (0.2)</td>
</tr>
<tr>
<td>CYP 2C9&lt;sub&gt;C144&lt;/sub&gt;/N-deisopropyl</td>
<td>1.3</td>
<td>1.6 (0.8)</td>
<td>0.5 (0.2)</td>
</tr>
<tr>
<td>CYP 2C9/5-OH</td>
<td>2.8</td>
<td>7.9 (2.9)</td>
<td>0.2 (0.3)</td>
</tr>
</tbody>
</table>
For tolbutamide 4-hydroxylation, which displayed monophasic Michaelis-Menten kinetics (Fig. 3), the maximal velocity \( V_{\text{max}} \) and Michaelis-Menten constant \( K_m \) were 17 nmol/h/mg and 160 \( \mu \)M, respectively. In the presence of fluvastatin (5 \( \mu \)M), there was an increase in \( K_m \) to 1.3 mM and only a relative small decrease in \( V_{\text{max}} \) as expected for a competitive inhibition. The mean inhibition constant \( K_i \) for three inhibitor concentrations was 0.3 \( \mu \)M. Diclofenac also exhibited monophasic Michaelis-Menten kinetics with a \( K_m \) of 9.4 \( \mu \)M and a \( V_{\text{max}} \) of 170 nmol/h/mg. \( K_m \) increased to 31 \( \mu \)M and \( V_{\text{max}} \) decreased to 95 nmol/h/mg in the presence of 1 \( \mu \)M fluvastatin. This is indicative of a mixed mode of inhibition with a mean \( K_i \) of 0.5 \( \mu \)M for three fluvastatin concentrations.

Glyburide metabolism in human liver microsomes exhibited monophasic Michaelis-Menten kinetics, with a \( V_{\text{max}} \) of 33 nmol/h/mg protein and a \( K_m \) of 8.4 \( \mu \)M. Several metabolites were detected, which correspond to hydroxylations at the phenylethyl moiety and at the cyclohexyl ring (Fischer et al., 1998). Fluvastatin selectively inhibited cyclohexyl hydroxylation of glyburide but had little effect on phenylethyl hydroxylation of glyburide. The inhibition of cyclohexyl hydroxylation of glyburide by fluvastatin was predominantly competitive as indicated by a 3-fold increase in \( K_m \) from 9 to 27 \( \mu \)M with only a \( \sim 30\% \) decrease in \( V_{\text{max}} \) from 320 to 230 nmol/h/mg for the highest 20 \( \mu \)M fluvastatin concentration. The \( K_i \) value was thus determined to be 5.9 \( \pm \) 0.8 \( \mu \)M. Sulfaphenazole, a specific inhibitor of CYP2C9, also specifically inhibited glyburide cyclohexyl hydroxylation with an \( IC_{50} \) of \( \sim 20 \mu M \) (data not shown).

Glibornuride was metabolized to four unidentified metabolites in incubations with human liver microsomes. Metabolism followed monophasic Michaelis-Menten kinetics
with a maximal velocity $V_{\text{max}}$ of 81 nmol/h/mg protein and a $K_m$ of 120 µM. In contrast with glyburide, the inhibition by fluvastatin of gliobronide metabolism was noncompetitive. The mean $K_m$ calculated was 9.4 ± 2.1 µM. Sulfaphenazole also inhibited gliobronide metabolism with an IC$_{50}$ of ~10 µM (data not shown).

**Discussion**

The combined data indicate that fluvastatin is metabolized by multiple enzymes. Specifically, the metabolites that are primarily responsible for the elimination of fluvastatin (Dain et al., 1993) are formed by several enzymes: 5-hydroxy-fluvastatin by CYP2C9 and 6-hydroxy- and desisopropyl-fluvastatin mainly by CYP2C9, CYP3A4, and CYP2C8. The most relevant enzyme for in vivo metabolic clearance of fluvastatin is predicted to be CYP2C9, because it is the only one forming all three metabolites found in vivo. All other enzymes capable of metabolizing fluvastatin produced only the 5-hydroxy-fluvastatin metabolite. The relative contribution of 6-hydroxy- and N-desisopropyl-fluvastatin could therefore serve as an indicator for the contribution of CYP2C9 to fluvastatin elimination. In four healthy human volunteers, the contribution of CYP2C9 appeared to be ~65% of fluvastatin elimination based on fecal metabolite profiles (Dain et al., 1993). CYP2C9 also appears to be responsible for the high $K_m$ component, which contributes 73 to 83% to total fluvastatin metabolism in human liver microsomes. The apparent $K_m$ for this component is similar to the $K_m$ for the inhibition of CYP2C9 substrates, such as tolbutamide and diclofenac, by fluvastatin. Also specific CYP2C9 inhibitors, such as sulfaphenazole (Baldwin et al., 1995), strongly inhibit 6-hydroxy- and N-desisopropyl-fluvastatin formation but only inhibited to a limited extent 5-hydroxy-fluvastatin formation. In contrast, ketoconazole, a specific inhibitor of CYP3A (Baldwin et al., 1995), inhibited only 5-hydroxy-fluvastatin formation. Furthermore, the ketoconazole concentration required for a 50% inhibition of 5-hydroxy-fluvastatin formation was greater than would be expected for a reaction that is catalyzed only by CYP3A. This suggests the involvement of enzymes other than CYP3A in this pathway.

For the individual enzymes, the $K_m$ of recombinant CYP2C9 fluvastatin metabolism corresponded most closely to the higher $K_m$ component in human liver microsomes, whereas the $K_m$ of recombinant CYP3A for fluvastatin exhibits a lower $K_m$ possibly reflecting the lower $K_m$ component observed in human liver. Both CYP2C9 and CYP3A would thus be predicted to be the major enzymes involved in fluvastatin metabolism.

Overall, fluvastatin appears to be metabolized in human liver by several enzymes, with CYP2C9 being the most important, followed by CYP3A4 and CYP2C8. There was no difference in fluvastatin intrinsic metabolic clearance for CYP2C9$_{R144}$ and the variant allele CYP2C9$_{C144P}$ which has been associated with a smaller warfarin maintenance dose in heterozygotes (Furuya et al., 1995). Based on the present data, no difference in fluvastatin clearance is expected in patients who express CYP2C9$_{C144P}$. The involvement of several enzymes in the metabolism of fluvastatin should minimize the effect, in case a coadministered compound inhibits one enzyme. Clinical observations confirm these findings. For example, neither CYP2C9 inhibitors/substrates such as the antiadibiotics tolbutamide and glyburide, the anticoagulant warfarin, or the proton pump inhibitor omeprazole (Appel and Dingemanse, 1996) nor CYP3A inhibitors/substrates such as the immunosuppressive cyclosporine A or the antifungal itraconazole had significant clinical effects on fluvastatin. Furthermore, even a compound such as isradipine, which inhibits both CYP2C9- and CYP3A-mediated pathways of fluvastatin metabolism in vitro, has not been able to clinically significantly affect, because isradipine plasma concentrations are >80-fold lower than the in vitro IC$_{50}$ values.

Fluvastatin appears also to be safe with respect to its potential effect on other compounds. Fluvastatin was previously reported to inhibit CYP2C9 but not CYP3A4 and CYP2D6 in vitro (Transon et al., 1996). The present data confirm these findings and demonstrate that fluvastatin does not inhibit CYP1A2, CYP2C8, CYP2C19, or CYP3A. Only small effects on coadministered CYP2C9 substrates were also observed in vivo, in spite of the relatively potent inhibition of CYP2C9 in vitro. Compounds such as diclofenac, warfarin, tolbutamide, or glyburide were only minimally affected, with only $C_{\text{max}}$ being increased (Transon et al., 1995; Appel and Dingemanse, 1996). This can be explained by the short terminal half-life of fluvastatin of 0.5 to 1 h, which would suggest that fluvastatin can inhibit CYP2C9 mainly during first-pass.

In summary, fluvastatin has a low potential for metabolic drug-drug interactions as compared to other HMG-CoA reductase inhibitors. Multiple enzymes are involved in the metabolism of fluvastatin, with CYP2C9 as the major one. Conversely, although fluvastatin is a potent inhibitor of CYP2C9, this effect is limited because of fluvastatin’s rapid systemic clearance. As a consequence, fluvastatin inhibits coadministered compounds’ metabolism only during first-pass.

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**References**


