# Plasma concentrations of active simvastatin acid are increased by gemfibrozil

*Background:* Concomitant treatment with simvastatin and gemfibrozil, two lipid-lowering drugs, has been associated with occurrence of myopathy in case reports. The aim of this study was to determine whether gemfibrozil affects the pharmacokinetics of simvastatin and whether it affects CYP3A4 activity in vitro.
*Methods:* A double-blind, randomized crossover study with two phases (placebo and gemfibrozil) was carried out. Ten healthy volunteers were given gemfibrozil (600 mg twice daily) or placebo orally for 3 days. On day 3 they ingested a single 40-mg dose of simvastatin. Plasma concentrations of simvastatin and simvastatin acid were measured up to 12 hours. In addition, the effect of gemfibrozil (0 to 1200 μmol/L) on midazolam 1´-hydroxylation, a CYP3A4 model reaction, was investigated in human liver microsomes in vitro.
*Results:* Gemfibrozil increased the mean total area under the plasma concentration–time curve of simvastatin [AUC(0-∞)] by 35% ($P < .01$) and the AUC(0-∞) of simvastatin acid by 185% ($P < .001$). The elimination half-life of simvastatin was increased by 74% ($P < .05$), and that of simvastatin acid was increased by 51% ($P < .01$) by gemfibrozil. The peak concentration of simvastatin acid was increased by 112%, from 3.20 ± 2.73 ng/mL to 6.78 ± 4.67 ng/mL (mean ± SD; $P < .01$). In vitro, gemfibrozil showed no inhibition of midazolam 1´-hydroxylation.
*Conclusions:* Gemfibrozil increases plasma concentrations of simvastatin and, in particular, its active form, simvastatin acid, suggesting that the increased risk of myopathy in combination treatment is, at least partially, of a pharmacokinetic origin. Because gemfibrozil does not inhibit CYP3A4 in vitro, the mechanism of the pharmacokinetic interaction is probably inhibition of non-CYP3A4–mediated metabolism of simvastatin acid. (Clin Pharmacol Ther 2000;68:122-9.)

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The combination of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) and a fibric acid derivative (fibrate), such as gemfibrozil, is a promising approach in the treatment of patients with mixed lipid abnormalities.[1-3] However, reports of severe myopathy in patients treated with a statin-fibrate combination have limited the widespread use of the combination.[2,4-8] It is generally believed that the skeletal muscle adverse effects of statins in combination with fibrates are based on a pharmacodynamic interaction, because statins and fibrates can cause myopathy also when administered alone.[9-14]

The risk of myopathy during treatment with lovastatin and simvastatin is dose- and plasma concentration–dependent.[12-14] Furthermore, the risk is markedly increased by concomitant treatment with CYP3A4-inhibiting drugs, such as itraconazole and cyclosporin (INN, ciclosporin), which increase the plasma concentrations of the statins.[9,15-20] Several cases of myopathy have been reported in patients receiving concomitant treatment with simvastatin and gemfibrozil,[2,7,8] but it is not known whether gemfibrozil affects the pharmacokinetics of simvastatin. Therefore we wanted to study the effects of gemfibrozil on the plasma concentrations of simvastatin and its active form, simvastatin acid, in healthy volunteers. In addition, because simvastatin is a CYP3A4 substrate,[21] the effect of gemfibrozil on mid-

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**Table I.** Characteristics of the subjects and the $C_{max}$ and AUC(0-12) values of gemfibrozil on day 3

| *Subject no.* | *Sex* | *Age (y)* | *Weight (kg)* | *Use of oral contraceptives* | *Gemfibrozil $C_{max}$ (mg/L)* | *Gemfibrozil AUC(0-12) (mg · h/L)* |
|---|---|---|---|---|---|---|
| 1 | Male | 21 | 81 | No | 35.6 | 88.0 |
| 2 | Male | 21 | 70 | No | 34.1 | 55.3 |
| 3 | Female | 20 | 54 | Yes* | 38.1 | 75.8 |
| 4 | Male | 21 | 65 | No | 31.2 | 75.7 |
| 5 | Female | 22 | 54 | No | 42.1 | 173.1 |
| 6 | Male | 31 | 68 | No | 29.1 | 74.8 |
| 7 | Female | 21 | 55 | Yes* | 35.0 | 136.2 |
| 8 | Male | 23 | 80 | No | 30.4 | 77.8 |
| 9 | Female | 21 | 41 | No | 63.3 | 281.5 |
| 10 | Female | 22 | 51 | No | 40.4 | 127.8 |

$C_{max}$, Observed peak concentration; AUC(0-12), area under the plasma concentration–time curve from 0 to 12 hours after the administration of simvastatin (ie, from 1 to 13 hours after the last dose of gemfibrozil).
*Ethinyl estradiol (INN, ethinylestradiol), 20 μg, + gestodene, 75 μg.

azolam 1´-hydroxylation, a CYP3A4 model reaction,[22] was investigated in human liver microsomes in vitro.

## METHODS

### Human pharmacokinetic study

***Subjects.*** The study protocol was approved by the Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki, and the Finnish National Agency for Medicines. Ten healthy volunteers participated in the study after each gave written informed consent (Table I). They were ascertained to be healthy by means of a physical examination and routine blood chemistry tests (including blood hemoglobin, serum creatinine, creatine kinase, alanine aminotransferase, γ-glutamyltransferase, alkaline phosphatase, and for women human chorionic gonadotropin as a pregnancy test). Two women were receiving oral contraceptive steroids, but none of the other volunteers was receiving any continuous medication. None of the subjects had a history of smoking.

***Protocol.*** The study was carried out according to a randomized, double-blind crossover design with two phases. The washout period between the study phases was 4 weeks. As pretreatments, the subjects received gemfibrozil 600 mg (one Lopid 600 mg tablet, Gödecke/Parke Davis, Freiburg, Germany) or placebo twice daily at 8 AM and 8 PM orally for 2 days, according to a randomization schedule. On day 3 the subjects ingested gemfibrozil 600 mg or placebo with water 150 mL at 8 AM and simvastatin 40 mg (one Zocor 40 mg tablet; Merck Sharp & Dohme, Haarlem, The Netherlands) with water 150 mL at 9 AM. The volunteers fasted overnight before administration of simvastatin and had a warm standard meal 3 hours and a light standard meal 7 hours afterward. The volunteers were not allowed to drink alcohol during the study days and the previous 48 hours or grapefruit juice during the study days and the previous 2 weeks.

***Blood sampling.*** On the days of administration of simvastatin, a plastic cannula was inserted into a forearm vein of each subject and kept patent with an obturator. Timed blood samples (10 mL each) were drawn into tubes containing ethylenediaminetetraacetic acid just before administration of simvastatin and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours later. Plasma was separated within 30 minutes and divided into 3 tubes, which were stored at –70°C until analysis.

***Determination of plasma simvastatin and simvastatin acid.*** The plasma concentrations of simvastatin and simvastatin acid were determined by use of liquid chromatography–tandem mass spectrometry, with a modification of a previously described method.[23] The system was equipped with a Perkin Elmer Series 2000 injector and binary pumps (Perkin Elmer, Concord, Ontario, Canada), a Waters Symmetry $C_8$ column (2.1 × 50 mm, 3.5 μm; Waters, Milford, Mass), and a Perkin Elmer SCIEX API 3000 LC-MS-MS system (Perkin Elmer). In brief, the internal standard lovastatin was added to tubes containing plasma 0.5 mL and ammonium acetate buffer 0.5 mL (50 mmol/L; pH 4.3). Thereafter the analytes and internal standard were extracted from plasma into acetonitrile containing 1% acetic acid, by use of Varian Bond Elut $C_{18}$ solid-phase extraction columns (Varian, Harbor City, Australia). After evaporation to dryness, the samples were reconstituted with 70:30 acetonitrile/ammonium acetate buffer (4 mmol/L; pH 4.3) and analyzed by turbo ion spray liquid chromatography–tandem mass spectrometry in the positive ion mode. A liquid chromatographic gradient elution was performed by combining eluent A

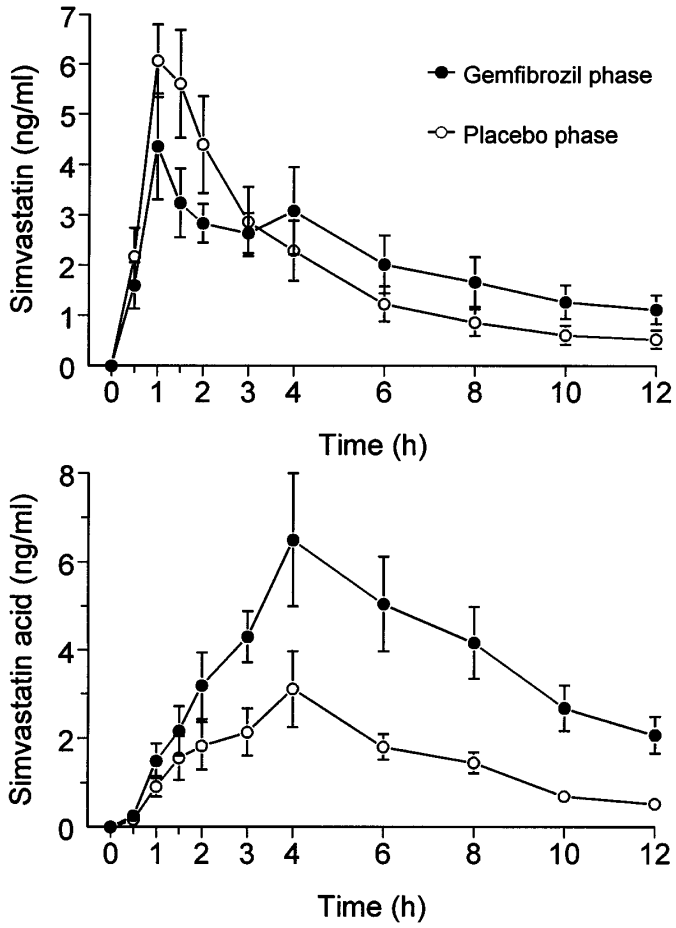


**Fig 1.** Plasma concentrations of simvastatin and simvastatin acid (mean ± SEM) in 10 healthy volunteers after a single oral dose of 40 mg simvastatin, after a 3-day pretreatment with gemfibrozil (600 mg twice daily), or placebo. *Open circles*, Concentrations during placebo administration; *solid circles*, concentrations during gemfibrozil administration.

(acetonitrile) and eluent B (4 mmol/L ammonium acetate, pH 4.3) in the following manner: at 0 minutes, 70% eluent A; at 0 to 1.6 minutes, a linear gradient from 70% to 100% eluent A; at 1.6 to 3.6 minutes, 100% eluent A; and at 3.6 to 14 minutes, 70% eluent A. The ion transitions monitored were *m/z* 437.3 to *m/z* 303.1 for simvastatin acid, *m/z* 436.4 (ammonium adduct) to *m/z* 285.3 for simvastatin, and *m/z* 405.2 to *m/z* 199.1 for lovastatin. The limit of quantification was 0.1 ng/mL for simvastatin and simvastatin acid, and the standard curves were linear for both analytes from 0.1 ng/mL to 100 ng/mL. The intraassay coefficients of variation were 1.8% at 0.12 ng/mL, 4.6% at 5.4 ng/mL, and 0.8% at 49.7 ng/mL for simvastatin, and 12.9% at 0.097 ng/mL, 9.8% at 5.1 ng/mL, and 3.9% at 51.0 ng/mL for simvastatin acid ($n = 3$).

***Determination of plasma gemfibrozil.*** Plasma concentrations of gemfibrozil were determined by use of HPLC with ultraviolet detection.[24] Ibuprofen was used as an internal standard. The limit of quantification was 0.1 mg/L, and the between-day coefficient of variation was less than 7% at relevant plasma gemfibrozil concentrations (n = 3).

***Pharmacokinetic calculations.*** The pharmacokinetics of the drugs were characterized, when appropriate, by peak concentrations in plasma ($C_{max}$), concentration peak times ($t_{max}$), elimination half-lives ($t_{½}$), and areas under the concentration–time curve from 0 to 12 hours [AUC(0-12)] and from 0 to infinity [AUC(0-∞)]. The $C_{max}$ and $t_{max}$ values were taken directly from the original data. The terminal log-linear part of the plasma drug concentration–time curve was identified visually

**Table II.** The pharmacokinetic variables of 40 mg simvastatin in 10 healthy subjects after a 3-day pretreatment with placebo or 600 mg gemfibrozil twice daily

| *Variable* | *Placebo phase (control)* | *Gemfibrozil phase* | *95% CI for the ratio of gemfibrozil to placebo* |
|---|---|---|---|
| *Simvastatin* | | | |
| $C_{max}$ (ng/mL) | 6.87 ± 3.30 | 6.15 ± 2.44 | 0.91 (0.60-1.37) |
| Relative to control | 1 | 0.81 (0.51-2.81) | — |
| $t_{max}$ (h) | 1 (0.5-1.5) | 1 (0.5-4) | — |
| $t_{½}$ (h) | 3.45 ± 0.94 | 5.99 ± 3.41* | 1.74 (1.19-2.28) |
| Relative to control | 1 | 1.65 (0.93-2.84) | — |
| AUC(0-12) (ng · h/mL) | 22.2 ± 14.4 | 24.8 ± 13.6 | 1.12 (0.88-1.42) |
| Relative to control | 1 | 1.16 (0.54-2.56) | — |
| AUC(0-∞) (ng · h/mL) | 25.2 ± 16.6 | 36.2 ± 23.8† | 1.35 (1.12-1.64) |
| Relative to control | 1 | 1.43 (0.56-2.37) | — |
| *Simvastatin acid* | | | |
| $C_{max}$ (ng/mL) | 3.20 ± 2.73 | 6.78 ± 4.67† | 2.18 (1.36-3.52) |
| Relative to control | 1 | 2.07 (0.64-7.38) | — |
| $t_{max}$ (h) | 4 (3-8) | 4 (2-8) | — |
| $t_{½}$ (h) | 3.02 ± 0.46 | 4.56 ± 1.30† | 1.51 (1.18-1.84) |
| Relative to control | 1 | 1.35 (0.84-2.45) | — |
| AUC(0-12) (ng · h/mL) | 17.7 ± 10.8 | 43.9 ± 23.2‡ | 2.49 (1.74-3.56) |
| Relative to control | 1 | 2.24 (0.94-7.23) | — |
| AUC(0-∞) (ng · h/mL) | 20.0 ± 11.9 | 58.2 ± 31.3‡ | 2.85 (1.99-4.10) |
| Relative to control | 1 | 2.50 (0.97-8.60) | — |
| *AUC(0-∞) ratio (simvastatin acid/simvastatin)* | 1.11 ± 1.30 | 2.33 ± 2.12* | 2.09 (1.10-3.09) |
| Relative to control | 1 | 1.90 (1.02-5.77) | — |

Data are mean values ± SD; $t_{max}$ and relative to control data are given as medians with ranges in parentheses.
95% CI, 95% Confidence interval for the ratio of gemfibrozil to placebo; $C_{max}$, observed peak concentration; $t_{max}$, observed time to reach peak concentration; AUC(0-12), area under the concentration versus time curve to 12 hours; AUC(0-∞), area under the concentration versus time curve to infinity; $t_{½}$, elimination half-life.
*$P < .05$, versus placebo phase.
†$P < .01$, versus placebo phase.
‡$P < .001$, versus placebo phase.

for each individual curve. The elimination rate constant ($k_e$) was determined by a linear regression analysis using the last 4 to 7 points on the plot of the natural logarithm of the plasma drug concentration–time curve. The $t_{½}$ was calculated by the equation: $t_{½} = \ln 2/k_e$. The AUC(0-12) and AUC(0-∞) were calculated by use of the linear trapezoidal rule for the rising phase and the log-linear trapezoidal rule for the descending phase with extrapolation to infinity, when appropriate, by dividing the last measured concentration by $k_e$. The AUC(0-12) of gemfibrozil, determined by the trapezoidal rule, refers to the time between 0 and 12 hours after the ingestion of simvastatin, that is, between 1 and 13 hours after the last dose of gemfibrozil.

***Statistical analysis.*** The data are expressed as mean values ± SD in the text and tables and as mean values ± SEM in the figures. Statistical comparisons of the pharmacokinetic variables (except $t_{max}$) for within-patient differences between gemfibrozil and placebo phases were carried out by use of repeated-measures ANOVA with treatment sequence and treatment as factors. Logarithmic transformation of $C_{max}$ and AUC values was done before statistical analysis. The 95% confidence intervals were calculated for the ratios of the variables between gemfibrozil and placebo phases. The Pearson product-moment correlation coefficient was used to investigate the possible relationship between the pharmacokinetic variables of gemfibrozil and simvastatin. The Wilcoxon signed-rank test was used for analysis of $t_{max}$. The analysis was performed with Systat for Windows, V6.0.1 (SPSS Inc, Chicago, Ill). A two-tailed *P* value was used, and the level of statistical significance was $P < .05$.

### In vitro study

***Material.*** Midazolam and 1´-hydroxymidazolam were kindly provided by Hoffmann-La Roche (Basel, Switzerland). NADPH was purchased from Sigma Chemical Co (St Louis, Mo). Other chemicals and reagents were obtained from Merck (Darmstadt, Germany).

***Human liver microsomes.*** Human adult liver samples (HL20 and HL23) were obtained from O. Pelkonen (Department of Pharmacology and Toxicology,

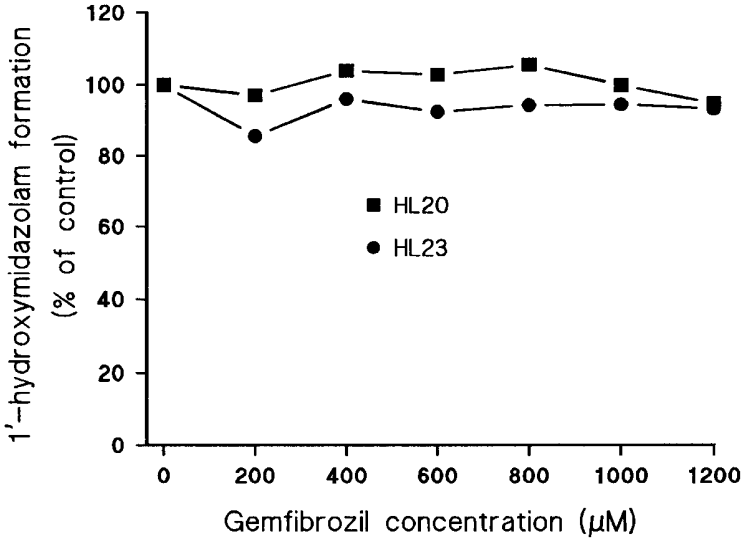


**Fig 2.** Effect of gemfibrozil on 1´-hydroxylation of midazolam by microsomes from two human livers (HL20 and HL23). Midazolam (6.25 μmol/L) was incubated with different concentrations of gemfibrozil. Values represent the average of duplicate determinations.

University of Oulu, Oulu, Finland) under a protocol approved by the local Ethics Committee. The microsomes were prepared as described previously.[25] Protein concentrations were determined colorimetrically by the method of Lowry et al.[26]

***Assay of midazolam 1´-hydroxylation.*** All incubations were performed in duplicate with a 0.2-mL incubation volume. In all experiments, gemfibrozil was dissolved in acetonitrile, and acetonitrile was first removed by evaporating to dryness. Gemfibrozil (0 to 1200 μmol/L) was then reconstituted with an incubation medium containing 0.13 mol/L sodium phosphate buffer (pH 7.4), 5.0 mmol/L magnesium chloride, 1.0 mmol/L NADPH, and 6.25 μmol/L midazolam. After incubation at 37°C for 2 minutes, the reaction was initiated by adding microsomal protein (100 μg/0.2 mL). In an additional experiment, gemfibrozil was first preincubated with the incubation medium and microsomes for 15 minutes, after which the reaction was started by adding midazolam. The formation of 1´-hydroxymidazolam was linear up to 8 minutes at 37°C, and an 8-minute incubation time was used. The reaction was stopped by adding 200 μL ice-cold methanol, containing 25 ng/mL methoxydiazepam as an internal standard. After centrifugation, the supernatant was subjected to analysis of 1´-hydroxymidazolam by HPLC as previously described.[27] The limit of quantification was 1 ng/mL, and the between-day coefficient of variation was less than 3% at relevant concentrations (n = 7).

## RESULTS

### Human pharmacokinetic study

***Pharmacokinetics of simvastatin.*** Gemfibrozil slightly increased the plasma concentrations of parent simvastatin and markedly elevated the concentrations of simvastatin acid, compared with placebo (Fig 1). During the gemfibrozil phase, the AUC(0-∞) of simvastatin was 35% larger ($P < .01$) and the $t_{½}$ 74% longer (5.99 ± 3.41 hours versus 3.45 ± 0.94 hours; $P < .05$) than during the placebo phase (Table II). Gemfibrozil had no statistically significant effect on the $C_{max}$ or $t_{max}$ of simvastatin. During the gemfibrozil phase, the AUC(0-∞) of simvastatin acid was 185% larger than during the placebo phase ($P < .001$). In addition, the $C_{max}$ of simvastatin acid was increased by 112% (from 3.20 ± 2.73 ng/mL to 6.78 ± 4.67 ng/mL; $P < .01$) and the $t_{½}$ by 51% (from 3.02 ± 0.46 hours to 4.56 ± 1.30 hours; $P < .01$) by gemfibrozil. Furthermore, the AUC(0-∞) ratio of simvastatin acid to simvastatin was more than doubled by gemfibrozil ($P < .05$).

***Pharmacokinetics of gemfibrozil.*** On the day of simvastatin administration, the $C_{max}$ of gemfibrozil ranged from 29 mg/L to 63 mg/L (Table I). There was a significant correlation between the AUC(0-12) of gemfibrozil and the difference between the gemfibrozil and placebo phases in the $C_{max}$ and AUC(0-12) of simvastatin acid ($r = 0.866$, $P = .001$, and $r = 0.708$, $P = .022$, respectively).

### In vitro study

Gemfibrozil showed no appreciable inhibitory effect on midazolam 1´-hydroxylation in human liver microsomes with gemfibrozil concentrations up to 1200 μmol/L either with (data not shown) or without preincubation (Fig 2).

## DISCUSSION

Simvastatin is an inactive lactone pro-drug, which is reversibly converted to active simvastatin acid by esterases and also nonenzymatically.[28] The oxidative metabolism of simvastatin to other metabolites is mediated primarily by CYP3A4,[21] and therefore inhibitors of CYP3A4 considerably increase the plasma concentrations of parent simvastatin.[15,17,19] CYP3A4 inhibitors do not prevent the conversion of simvastatin to the acid form. However, interactions between CYP3A4 inhibitors and simvastatin result in somewhat smaller relative increases in the AUC values of simvastatin acid than those of parent simvastatin. For example, erythromycin increased the AUC of simvastatin and simvastatin acid 6.2-fold and 3.9-fold, respectively.[17] Also high doses of grapefruit juice increased more the AUC of simvastatin (16-fold) than that of simvastatin acid (sevenfold).[29]

In this study, administration of the usual therapeutic doses of gemfibrozil (600 mg twice daily) for 3 days approximately tripled the total AUC of simvastatin acid in healthy volunteers but increased the total AUC of parent simvastatin by 35% only. This difference in the effect of gemfibrozil on the pharmacokinetics of simvastatin and simvastatin acid was also reflected in the AUC ratio (simvastatin acid/simvastatin), which was doubled by gemfibrozil. In our in vitro studies, gemfibrozil was found not to inhibit the CYP3A4-mediated 1´-hydroxylation of midazolam in human liver microsomes even at 1200 μmol/L, which is about 10 times as high as the $C_{max}$ of gemfibrozil in our volunteer study. These findings strongly suggest that the observed pharmacokinetic interaction was the result of the effect of gemfibrozil on non-CYP3A4–mediated elimination pathways of simvastatin acid. This conclusion is also in line with two studies in kidney transplant recipients, which showed that gemfibrozil had no effect on[30] or even slightly decreased the blood concentrations of cyclosporine (INN, ciclosporin),[31] a well-known CYP3A4 and P-glycoprotein substrate. However, because the enzymes responsible for the metabolism of simvastatin acid in human beings have not been fully characterized, the exact mechanism of the observed effects of gemfibrozil remains unclear.

Several cases of myopathy have been reported in patients receiving simvastatin with gemfibrozil.[2,7,8] It seems that the mechanism of skeletal muscle toxicity of statins is related to their mechanism of action, inhibition of HMG-CoA reductase.[16] The concentration of HMG-CoA reductase inhibitory activity in the muscle cells (and not in plasma) is probably the main determinant of this adverse effect, because the lipophilicity (the ability to penetrate into muscle cells) of statins seems to be crucial to their concentration-dependent muscle toxicity.[32,33] Although the plasma HMG-CoA reductase inhibitory activity was not determined in our study, it is reasonable to assume that the concentrations of active HMG-CoA reductase inhibitors (especially in the muscle cells) are increased by gemfibrozil, because the concentrations of the active form, simvastatin acid, were increased more than those of simvastatin. Furthermore, the CYP3A4-mediated formation of other active metabolites of simvastatin[21] probably remains unaffected by gemfibrozil, because it had no effect on CYP3A4 activity in vitro even in high concentrations. Thus these results suggest that the increased risk of myopathy during treatment with gemfibrozil and simvastatin in combination is, at least partially, of a pharmacokinetic origin. On the other hand, a pharmacodynamic interaction may also be involved because both agents can cause myopathy also when administered alone.[9-14]

The magnitude of the present, on average 185% increase in the total AUC of simvastatin acid caused by gemfibrozil is small when compared with the effects of potent CYP3A4 inhibitors such as itraconazole,[19] which substantially increase the risk of myopathy during treatment with simvastatin.[9,16,20] On the other hand, whereas CYP3A4 inhibitors increase the plasma concentration of active simvastatin acid, they reduce the CYP3A4 dependent formation of other active metabolites, which contribute significantly to the plasma HMG-CoA reductase inhibitory activity. The overall risk of myopathy during concomitant treatment with gemfibrozil and simvastatin is difficult to estimate, because published clinical studies have included a relatively small number of patients.[1,2] It should be noted, however, that there was considerable interindividual variability in the extent of the pharmacokinetic interaction between gemfibrozil and simvastatin, and in some individuals the total AUC of simvastatin acid was increased by a factor of eight. Moreover, in patients with elevated gemfibrozil concentrations (eg, patients with renal dysfunction) the risk of myopathy may be high, because the extent of the interaction seemed to depend on plasma gemfibrozil concentrations.

It is likely that gemfibrozil does not alter the pharmacokinetics of all statins; in fact, in one study gemfibrozil had no effect on the plasma concentrations of

fluvastatin,[34] which is metabolized mainly by CYP2C9. In a recent study, a single dose of fenofibrate did not affect the concentrations of pravastatin, but slightly increased the total AUC of its metabolite, 3α-hydroxy-isopravastatin.[35] However, it seems that there are no other published studies about possible pharmacokinetic interactions between fibrates and statins. Therefore more studies should be carried out to characterize the effects of gemfibrozil and other fibrates on the pharmacokinetics of different statins.

In conclusion, although gemfibrozil only slightly increases plasma concentrations of parent simvastatin, it considerably elevates the concentrations of active simvastatin acid, suggesting that the increased risk of myopathy in combination treatment is, at least partially, of a pharmacokinetic origin. Because gemfibrozil does not inhibit CYP3A4 in vitro, the mechanism of the pharmacokinetic interaction is probably inhibition of non-CYP3A4–mediated metabolism of simvastatin acid. Caution should be exercised when gemfibrozil and simvastatin are coadministered.

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