Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites

Background: **The pharmacokinetic interactions of the widely used statin atorvastatin with fibrates and enzyme inducers are not known. Therefore we studied the effects of rifampin (INN, rifampicin) and gemfibrozil on the pharmacokinetics of atorvastatin.**

Methods: **Two randomized crossover studies were conducted. In study 1, 10 healthy volunteers took 600 mg rifampin or placebo once daily for 5 days. On day 6, they ingested a single 40-mg dose of atorvastatin. In study 2, 10 healthy volunteers took 600 mg gemfibrozil or placebo twice daily for 5 days. On day 3, they ingested a single 20-mg dose of atorvastatin. Plasma concentrations of atorvastatin (in nanograms per milliliter) and its metabolites (in arbitrary units) were measured by liquid chromatography–tandem mass spectrometry up to 48 to 72 hours after dosing.**

Results: **Rifampin reduced the total area under the plasma concentration–time curve (AUC) of unchanged atorvastatin (acid) by 80% (95% confidence interval [CI], 73% to 84%; $P < .001$), that of the active metabolites 2-hydroxyatorvastatin acid by 43% (95% CI, 29% to 51%; $P < .001$) and 4-hydroxyatorvastatin acid by 81% (95% CI, 74% to 84%; $P < .001$), and that of their lactones by 93% (95% CI, 90% to 95%), by 61% (95% CI, 50% to 69%), and by 76% (95% CI, 70% to 81%), respectively ($P < .001$). The peak plasma concentration of 2-hydroxyatorvastatin acid was increased by 68% (95% CI, 21% to 127%; $P = .005$) by rifampin. Rifampin shortened ($P < .001$) the half-lives of atorvastatin (by 74%; 95% CI, 67% to 81%) and its metabolites, for example, atorvastatin lactone (by 82%; 95% CI, 80% to 85%) and 2-hydroxyatorvastatin acid (by 70%; 95% CI, 64% to 78%). Gemfibrozil increased the AUC of atorvastatin (by 24%; 95% CI, –1% to 50%; $P = .059$), 2-hydroxyatorvastatin acid (by 51%; 95% CI, 28% to 70%; $P < .001$) and its lactone (by 29%; 95% CI, 13% to 53%; $P = .003$), and 4-hydroxyatorvastatin acid (by 82%; 95% CI, 60% to 126%; $P < .001$) and its lactone (by 28%; 95% CI, 15% to 51%; $P = .001$). The half-lives of atorvastatin and its lactone metabolites were slightly shortened by gemfibrozil ($P < .05$).**

Conclusions: **Rifampin markedly decreases and gemfibrozil moderately increases the plasma concentrations of atorvastatin and its metabolites. It is advisable to increase the dosage of atorvastatin and preferable to administer it in the evening to guarantee adequate concentrations during the nighttime rapid cholesterol synthesis when rifampin or other potent inducers of cytochrome P450 3A4 are coadministered. Care is warranted, and only low doses of atorvastatin should be used if coadministration with gemfibrozil is needed. (Clin Pharmacol Ther 2005;78:154-67.)**

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Atorvastatin is one of the most widely used 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins). It is administered as the active hydroxy acid form, which is well absorbed but subject to

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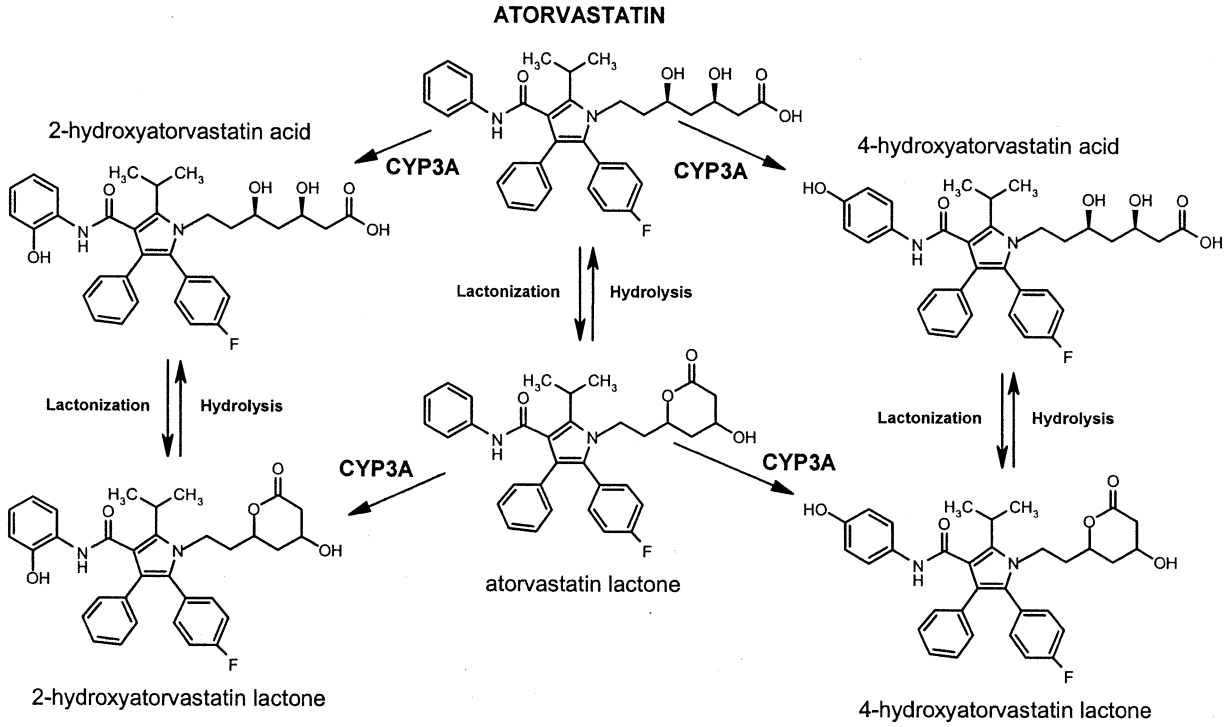

Fig 1. Structures of atorvastatin and its metabolites and proposed metabolic pathways of atorvastatin.[4]

substantial first-pass metabolism, leading to an oral bioavailability of about 14%.[1] Atorvastatin (acid) is biotransformed to atorvastatin lactone, which has been proposed to occur via a coenzyme A–dependent or an acyl glucuronide intermediate pathway (Fig 1).[2,3] Both atorvastatin and its lactone form are metabolized primarily by cytochrome P450 (CYP) 3A4 to hydroxylated metabolites, but CYP2C8 has also been shown to metabolize atorvastatin at a low rate.[4] The lactone forms of atorvastatin and its metabolites can also be hydrolyzed to their acid forms nonenzymatically or by esterases and paraoxonases.[1,2,5] In addition, atorvastatin seems to be a substrate for several transport proteins including the efflux transporter P-glycoprotein,[6,7] the uptake transporters organic anion transporting polypeptide 1B1 (OATP1B1; also known as OATP2, OATP-C, and LST-1),[8] and possibly a proton–monocarboxylic acid cotransporter (MCT).[6] The hydroxy acid forms of the main metabolites, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin,[1,9-11] are pharmacologically active and significantly contribute to the plasma HMG-CoA reductase inhibitory activity during atorvastatin treatment.[1]

Atorvastatin seems to be less susceptible to drug interactions with inhibitors of CYP3A4 than are lovastatin and simvastatin, which are administered in the inactive lactone form and have an extensive first-pass metabolism.[9] For example, itraconazole raised the area under the plasma concentration–time curve (AUC) of simvastatin acid by more than 15-fold[12] and the AUC of atorvastatin (acid) by only 3.3-fold.[10] Potent enzyme inducers, such as rifampin (INN, rifampicin) and carbamazepine,[13-15] reduce the AUC of simvastatin acid by about 85% to 95%.[16,17] On the basis of a case report, inducers of CYP enzymes (phenytoin) can reduce the cholesterol-lowering efficacy of both simvastatin and atorvastatin.[18] However, there seem to be no published studies about the effects of enzyme inducers on the pharmacokinetics of atorvastatin.

Fibric acid derivatives, such as gemfibrozil, are often coprescribed with statins for patients with mixed lipid disorders because of their complementary effects.[19] However, their coadministration is limited by an increased risk of myopathy, which is particularly high with the cerivastatin-gemfibrozil combination.[20-26] Recent evidence indicates that, in addition to pharmacodynamic interactions, pharmacokinetic mechanisms can contribute to gemfibrozil-statin interactions. Gemfibrozil has been shown to increase the plasma concentrations of several statins despite their different phar-

macokinetic characteristics.[27-31] These effects of gemfibrozil can be explained by inhibition of CYP2C8 and of transport proteins; in addition, inhibition of glucuronidation could be possible.[29-35] Myopathy and rhabdomyolysis have also been reported during concomitant administration of gemfibrozil and atorvastatin.[36] However, the possibility of a pharmacokinetic interaction between gemfibrozil and atorvastatin has not been studied previously.

Our aim was to investigate the effects of gemfibrozil and the prototypical inducer of CYP enzymes, rifampin, on the pharmacokinetics and metabolic pathways of atorvastatin.

METHODS

Subjects and study design. The study protocols were approved by the Ethics Committee for Studies in Healthy Subjects and Primary Care, Helsinki and Uusimaa Hospital District, and by the National Agency for Medicines. Two groups of 10 healthy volunteer subjects participated in 2 separate randomized crossover studies after giving written informed consent. The number of subjects (N = 10) was estimated to be sufficient to detect a 30% change in the AUC from time 0 to infinity [AUC(0-∞)] of atorvastatin (SD of difference, 30%) with a statistical power of 80% (α level, 5%). Study 1 comprised 6 male and 4 female subjects. Their mean age (±SD) was 25 ± 4 years (range, 18-31 years), and their mean weight was 68 ± 9 kg (range, 55-78 kg). Study 2 comprised 6 male and 4 female subjects. Their mean age was 23 ± 2 years (range, 20-26 years), and their mean weight was 73 ± 14 kg (range, 55-105 kg). None of the subjects was a tobacco smoker or used any continuous medication. All subjects were healthy on the basis of a medical history, physical examination, and routine laboratory test results.

In study 1 the volunteers took 600 mg rifampin (one 600-mg tablet of Rimapen; Orion Pharma, Espoo, Finland) or placebo orally once daily at 4 PM for 5 days. On day 6, after an overnight fast, a single oral dose of 40 mg atorvastatin (one 40-mg tablet of Lipitor; Pfizer, Freiburg, Germany) was administered with 150 mL water at 9 AM. In study 2 the volunteers took 600 mg gemfibrozil (one 600-mg tablet of Lopid; Parke-Davis, Freiburg, Germany) or placebo orally twice daily at 8 AM and 8 PM for 4 days and at 8 AM on day 5. On day 3, after an overnight fast, a single oral dose of 20 mg atorvastatin (one 20-mg tablet of Lipitor) was administered with 150 mL water at 9 AM. Food intake on days of administration of atorvastatin was standardized and comprised a warm meal 3 hours after atorvastatin intake and a light meal after 7 hours. The washout period between the phases was 4 weeks in study 1 and 2 weeks in study 2. Alcohol or strenuous exercise was not allowed for 2 days and grapefruit beverages or any drugs were not allowed for 1 week before the test days.

Sampling. On the days of administration of atorvastatin, a forearm vein of each subject was cannulated with a plastic cannula and kept patent with a stylet. Timed blood samples (10 mL each) were drawn into tubes that contained ethylenediaminetetraacetic acid before the administration of atorvastatin and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 34, and 48 hours later. In addition, 1 blood sample was taken at 72 hours after dosing in study 2. Plasma was separated within 30 minutes after sampling and stored at −70°C until analysis of atorvastatin and its metabolites and, as appropriate, gemfibrozil.

Determination of drug concentrations. The concentrations of atorvastatin and its main metabolites were measured by use of the liquid chromatography–tandem mass spectrometer PE SCIEX API 3000 (Sciex Division of MDS, Toronto, Ontario, Canada) operating in positive turbo ion spray mode as previously described[37] with some modifications. Chromatography was performed on a Symmetry C8 column (50 × 2.1 mm, internal diameter; 3.5 μm) protected by a Symmetry C8 guard column (10 × 2.1 mm, internal diameter; 3.5 μm) (Waters, Milford, Mass) by use of a gradient of 5-mmol/L ammonium acetate (pH 5.0, adjusted with glacial acetic acid) and acetonitrile. Cerivastatin was used as an internal standard. The samples were analyzed via selected reaction monitoring by use of the transition of the $[M+H]^+$ precursor ion to a product ion for each analyte and internal standard. The ion transitions monitored were mass-to-charge ratio (*m/z*) 559 to *m/z* 440 for atorvastatin, *m/z* 541 to *m/z* 448 for atorvastatin lactone, *m/z* 575 to *m/z* 440 for 2-hydroxyatorvastatin acid, *m/z* 557 to *m/z* 448 for 2-hydroxyatorvastatin lactone, *m/z* 575 to *m/z* 440 for 4-hydroxyatorvastatin acid, *m/z* 557 to *m/z* 448 for 4-hydroxyatorvastatin lactone, and *m/z* 460 to *m/z* 356 for cerivastatin. The limit of quantification for atorvastatin was 0.05 ng/mL, and the day-to-day coefficient of variation was below 11% at relevant concentrations (n = 5). Gemfibrozil and rifampin did not interfere with the assay. Atorvastatin metabolite concentrations are given in arbitrary units (units per milliliter) relative to the ratio of the peak height of each metabolite to that of the internal standard in the chromatogram. Plasma gemfibrozil concentrations were measured by HPLC with ultraviolet detection.[38] The

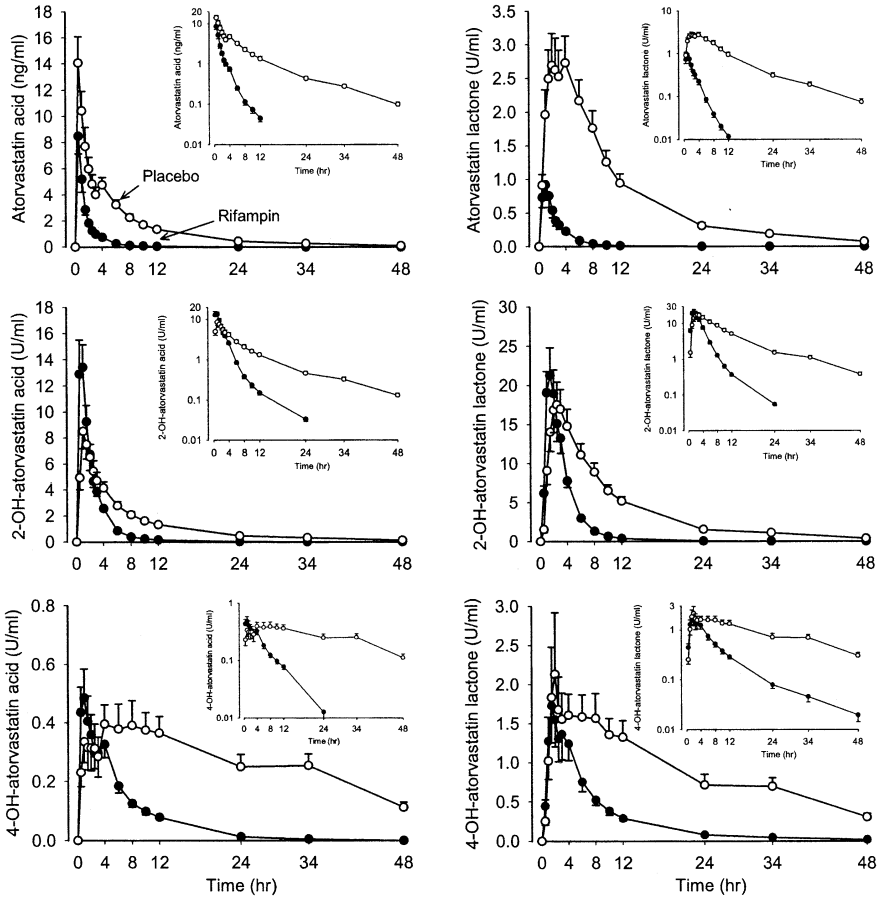

Fig 2. Mean (±SEM) plasma concentrations of atorvastatin, atorvastatin lactone, 2–hydroxy (OH) atorvastatin acid, 2-hydroxyatorvastatin lactone, 4-hydroxyatorvastatin acid, and 4-hydroxyatorvastatin lactone in 10 healthy volunteers after single oral dose of 40 mg atorvastatin after 5-day treatment with placebo or 600 mg rifampin once daily. *Insets* depict the same data on a semilogarithmic scale. *Open circles* indicate placebo phase; *solid circles* indicate rifampin phase.

limit of quantification was 0.1 mg/L, and the between-day coefficient of variation was below 4% at relevant concentrations (n = 5).

Pharmacokinetics. Peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), AUC from time 0 to 48 hours [AUC(0-48)] or AUC from time 0 to 72 hours [AUC(0-72)], AUC(0-∞), and elimination half-life ($t_{½}$) were calculated for atorvastatin and its metabolites. The terminal log-linear part of the concentration-time curve was identified visually for each curve. The elimination rate constant (k_e) was determined by linear regression analysis of the log-linear part of the concentration-time curve, and the elimination half-life was calculated by the following equation: $t_{½} = \ln 2/k_e$. The AUC values were calculated by a combination of the linear and log-linear trapezoidal rules, with extrapolation to infinity when appropriate, by dividing the last measured concentration by k_e. The pharmacokinetics of gemfibrozil was characterized by C_{max}, and AUC from time 0 to 11 hours [AUC(0-11)].

Statistical analysis. Results are expressed as mean ± SD in the text and tables and, for clarity, as mean ± SEM in Figs 2 and 4. The pharmacokinetic variables after the 2 pretreatments were compared by use of a paired t test or, in the case of t_{max}, by the Wilcoxon signed rank test. Logarithmic transformation of C_{max}, $t_{½}$, and AUC values was performed before statistical analysis, and 95% confidence intervals were calculated for the geometric mean ratios (rifampin or gemfibrozil phase value as a percentage of the control phase value) of these variables. All of the data were analyzed with the statistical program Systat for Windows, version

Table I. Pharmacokinetic variables of atorvastatin and its metabolites in 10 healthy subjects after single 40-mg dose of atorvastatin after 5-day treatment with 600 mg rifampin or placebo twice daily

Variable	*Placebo phase (control)*	*Rifampin phase*	*Rifampin phase (% of control)*	
			Mean and range	*95% CI*
Atorvastatin (acid)				
C_{max} (ng/mL)	15.8 ± 5.4	9.5 ± 3.7†	60% (34%-104%)	45%-81%
t_{max} (h)	0.5 (0.5-1.5)	0.5 (0.5-1)	—	
$t_{½}$ (h)	10.3 ± 1.2	2.7 ± 0.9‡	26% (14%-46%)	19%-33%
AUC(0-48) (ng × h/mL)	62.5 ± 20.7	12.6 ± 3.2‡	20% (12%-40%)	16%-27%
AUC(0-∞) (ng × h/mL)	64.0 ± 21.3	12.6 ± 3.2‡	20% (12%-39%)	16%-27%
Atorvastatin lactone				
C_{max} (U/mL)	2.9 ± 1.4	1.0 ± 0.7‡	35% (10%-62%)	21%-50%
t_{max} (h)	4 (1.5-6)	0.5 (0.5-1.5)†	—	
$t_{½}$ (h)	11.7 ± 1.9	2.1 ± 0.6‡	18% (12%-22%)	15%-20%
AUC(0-48) (U × h/mL)	33.5 ± 14.7	2.6 ± 1.5‡	8% (4%-17%)	5%-10%
AUC(0-∞) (U × h/mL)	34.8 ± 15.1	2.6 ± 1.5‡	7% (4%-17%)	5%-10%
2-Hydroxyatorvastatin acid				
C_{max} (U/mL)	9.8 ± 4.1	16.5 ± 7.1†	168% (76%-297%)	121%-227%
t_{max} (h)	1 (0.5-2)	0.5 (0.5-1)	—	
$t_{½}$ (h)	11.8 ± 1.0	3.5 ± 0.9‡	30% (14%-45%)	22%-36%
AUC(0-48) (U × h/mL)	57.0 ± 19.1	34.0 ± 7.4‡	60% (38%-87%)	51%-74%
AUC(0-∞) (U × h/mL)	59.2 ± 19.8	34.0 ± 7.4‡	57% (36%-82%)	49%-71%
2-Hydroxyatorvastatin lactone				
C_{max} (U/mL)	17.8 ± 9.0	22.0 ± 11.3	123% (51%-206%)	87%-165%
t_{max} (h)	2.75 (2.5-4)	1.5 (1-1.5)†	—	
$t_{½}$ (h)	12.0 ± 2.1	4.0 ± 0.8‡	33% (23%-48%)	27%-39%
AUC(0-48) (U × h/mL)	180.7 ± 72.5	73.4 ± 26.5‡	41% (21%-57%)	33%-52%
AUC(0-∞) (U × h/mL)	187.4 ± 73.7	73.5 ± 26.5‡	39% (21%-55%)	31%-50%
4-Hydroxyatorvastatin acid				
C_{max} (U/mL)	0.50 ± 0.27	0.61 ± 0.31	122% (52%-240%)	79%-181%
t_{max} (h)	5 (1.5-12)	1 (0.5-4)†	—	
$t_{½}$ (h)	25.6 ± 7.1	5.3 ± 1.3‡	21% (14%-31%)	17%-25%
AUC(0-48) (U × h/mL)	12.8 ± 6.3	3.2 ± 1.2‡	25% (14%-51%)	20%-35%
AUC(0-∞) (U × h/mL)	17.0 ± 8.4	3.2 ± 1.2‡	19% (10%-35%)	16%-26%
4-Hydroxyatorvastatin lactone				
C_{max} (U/mL)	2.6 ± 2.4	1.9 ± 1.4	72% (40%-337%)	46%-116%
t_{max} (h)	4 (1.5-8)	2 (1.5-4)*	—	
$t_{½}$ (h)	21.3 ± 4.4	8.0 ± 2.5‡	38% (22%-59%)	31%-45%
AUC(0-48) (U × h/mL)	42.8 ± 22.0	12.5 ± 6.4‡	29% (15%-48%)	23%-37%
AUC(0-∞) (U × h/mL)	52.4 ± 25.4	12.8 ± 6.5‡	24% (14%-36%)	19%-30%

Values are shown as mean ± SD unless otherwise indicated; t_{max} data are shown as median and range.

CI, Confidence interval; C_{max}, peak plasma concentration; t_{max}, time to peak plasma concentration; $t_{½}$, elimination half-life; AUC(0-48), area under plasma concentration–time curve from time 0 to 48 hours; AUC(0-∞), area under plasma concentration–time curve from time 0 to infinity.

*$P < .05$.

†$P < .005$.

‡$P < .0005$.

6.0.1 (SPSS, Chicago, Ill). Differences were considered statistically significant at $P < .05$.

RESULTS

Study 1: Effect of rifampin on pharmacokinetics of atorvastatin. Rifampin decreased the AUC(0-∞) and $t_{½}$ of unchanged atorvastatin (acid) and its metabolites (Fig 2 and Table I). The AUC(0-∞) of atorvastatin was decreased by 80% (range, 61% to 88%; $P < .001$) and the C_{max} was decreased by 40% (range, −4% to 66%) by rifampin compared with the placebo phase ($P = .003$). The AUC(0-∞) values of the active metabolites 2-hydroxyatorvastatin acid and 4-hydroxyatorvastatin acid were 43% (range, 18% to 64%) and 81% (range, 65% to 90%) smaller during the rifampin phase than during the control phase ($P < .001$). However, the C_{max} of

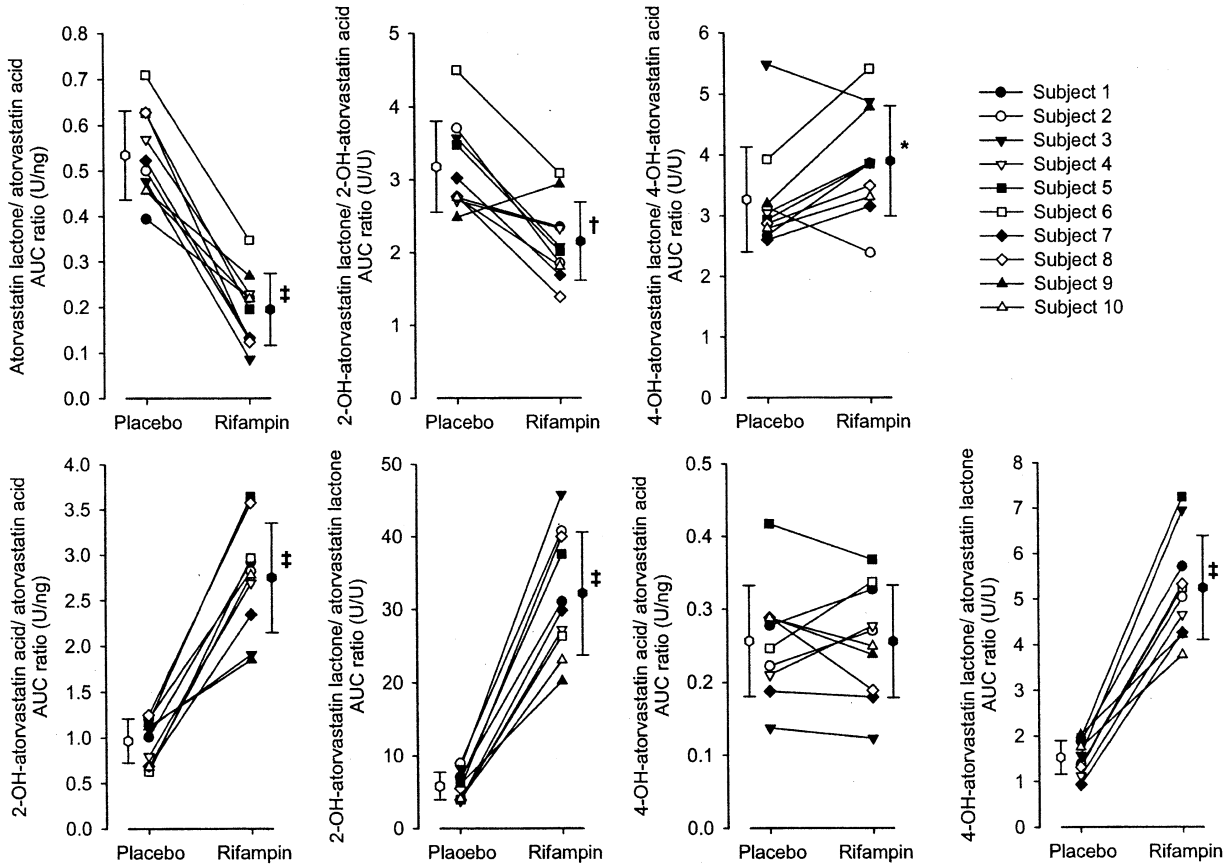

Fig 3. Individual and mean (±SD) area under plasma concentration–time curve from time 0 to infinity (AUC) ratios of atorvastatin, atorvastatin lactone, 2-hydroxyatorvastatin acid, 2-hydroxyatorvastatin lactone, 4-hydroxyatorvastatin acid, and 4-hydroxyatorvastatin lactone in 10 healthy volunteers after single oral dose of 40 mg atorvastatin after 5-day treatment with placebo or 600 mg rifampin once daily. *Asterisk*, P < .05; *dagger*, P < .005; *double dagger*, P < .0005.

2-hydroxyatorvastatin acid was increased by 68% (range, −24% to 197%; $P = .005$) by rifampin, reflecting induction of the first-pass metabolism of atorvastatin. Rifampin considerably shortened the half-lives of atorvastatin, 2-hydroxyatorvastatin acid, and 4-hydroxyatorvastatin acid (by 74%, 70%, and 79%, respectively; $P < .001$), and greatly decreased their 12-hour postdose concentration (by 97%, 89%, and 78%, respectively; $P < .001$) (Fig 2).

The AUC(0-∞) values of atorvastatin lactone, 2-hydroxyatorvastatin lactone, and 4-hydroxyatorvastatin lactone were reduced by 93%, 61%, and 76%, respectively, and their half-lives were greatly shortened by rifampin ($P < .001$) (Table I). In addition, the C_{max} of atorvastatin lactone was reduced by rifampin. The C_{max} of all measured lactone forms and 4-hydroxyatorvastatin acid was reached earlier during the rifampin phase than during the control phase ($P < .05$).

The lactone/acid AUC ratios of atorvastatin and 2-hydroxyatorvastatin were decreased (by 62% and 32%, respectively; $P < .005$) (Fig 3), whereas the lactone/acid AUC ratio of 4-hydroxyatorvastatin was increased (by about 20%, $P = .028$) by rifampin. The AUC ratios of 2-hydroxyatorvastatin lactone and 4-hydroxyatorvastatin lactone to atorvastatin lactone and the AUC ratio of 2-hydroxyatorvastatin acid to atorvastatin were increased several-fold by rifampin ($P < .001$), but the AUC ratio of 4-hydroxyatorvastatin acid to atorvastatin was unaltered.

Study 2: Effect of gemfibrozil on pharmacokinetics of atorvastatin. Gemfibrozil raised the plasma concentrations of parent atorvastatin and of both the acid and lactone forms of the 2-hydroxy and 4-hydroxy metab-

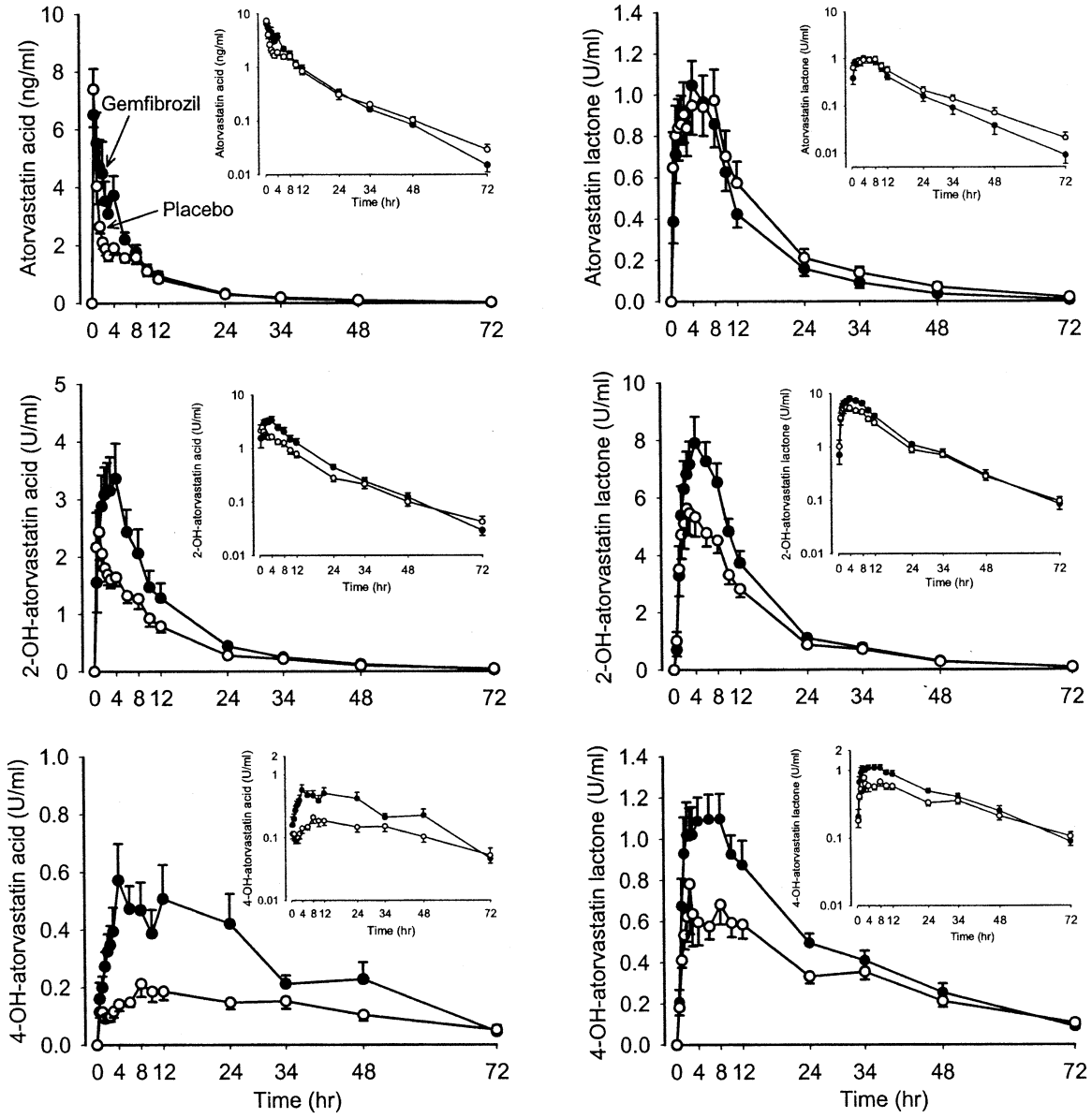

Fig 4. Mean (±SEM) plasma concentrations of atorvastatin, atorvastatin lactone, 2-hydroxyatorvastatin acid, 2-hydroxyatorvastatin lactone, 4-hydroxyatorvastatin acid, and 4-hydroxyatorvastatin lactone in 10 healthy volunteers after single oral dose of 20 mg atorvastatin on day 3 of 5-day treatment with placebo or 600 mg gemfibrozil twice daily. *Insets* depict the same data on a semilogarithmic scale. *Open circles* indicate placebo phase; *solid circles* indicate gemfibrozil phase.

olites but had no such effect on the concentrations of atorvastatin lactone (Fig 4 and Table II). During the gemfibrozil phase, the AUC(0-∞) of atorvastatin was 24% greater than during the placebo phase (range, −24% to 60%; P =.059). The AUC(0-∞) values of 2-hydroxyatorvastatin acid and 4-hydroxyatorvastatin acid were increased by 51% (range, −1% to 82%) and 82% (range, 38% to 182%) by gemfibrozil ($P < .001$), whereas those of the respective lactone forms were increased slightly less, by 29% and 28% ($P < .005$). In

Table II. Pharmacokinetic variables of atorvastatin and its metabolites in 10 healthy subjects after single 20-mg dose of atorvastatin on day 3 of 5-day treatment with 600 mg gemfibrozil or placebo twice daily

			Gemfibrozil phase (% of control)	
Variable	*Placebo phase*	*Gemfibrozil phase*	*Mean and range*	*95% CI*
Atorvastatin (acid)				
C_{max} (ng/mL)	8.2 ± 3.5	9.6 ± 4.0	117% (31%-227%)	>77%-184%
t_{max} (h)	0.5 (0.5-2.5)	0.75 (0.5-2)	—	
$t_{½}$ (h)	10.7 ± 2.2	9.0 ± 1.77†	84% (69%-109%)	77%-92%
AUC(0-72) (ng × h/mL)	34.7 ± 11.5	43.3 ± 15.7	125% (76%-161%)	100%-152%
AUC(0-∞) (ng × h/mL)	35.2 ± 11.8	43.6 ± 15.8	124% (76%-160%)	99%-150%
Atorvastatin lactone				
C_{max} (U/mL)	1.1 ± 0.5	1.1 ± 0.4	99% (40%-151%)	78%-135%
t_{max} (h)	2.5 (0.5-8)	4 (4-8)	—	
$t_{½}$ (h)	12.0 ± 2.2	9.6 ± 2.2‡	80% (59%-90%)	73%-87%
AUC(0-72) (U × h/mL)	18.5 ± 9.9	15.2 ± 7.3	82% (45%-114%)	71%-103%
AUC(0-∞) (U × h/mL)	18.9 ± 10.3	15.3 ± 7.5	81% (44%-114%)	71%-102%
2-Hydroxyatorvastatin acid				
C_{max} (U/mL)	3.1 ± 1.3	4.0 ± 1.7	129% (38%-183%)	89%-184%
t_{max} (h)	1 (0.5-4)	1.75 (0.5-6)	—	
$t_{½}$ (h)	12.4 ± 1.9	11.2 ± 2.2	90% (66%-119%)	79%-102%
AUC(0-72) (U × h/mL)	28.7 ± 10.0	44.1 ± 19.0‡	153% (99%-187%)	130%-173%
AUC(0-∞) (U × h/mL)	29.6 ± 10.7	44.6 ± 19.2‡	151% (99%-182%)	128%-170%
2-Hydroxyatorvastatin lactone				
C_{max} (U/mL)	6.1 ± 2.5	8.3 ± 2.8*	136% (59%-225%)	107%-182%
t_{max} (h)	4 (2-8)	4 (2-8)	—	
$t_{½}$ (h)	13.0 ± 2.7	11.3 ± 2.1*	87% (70%-105%)	79%-95%
AUC(0-72) (U × h/mL)	89.1 ± 28.5	116.1 ± 30.9†	130% (78%-180%)	114%-155%
AUC(0-∞) (U × h/mL)	91.0 ± 29.5	117.6 ± 31.9†	129% (78%-178%)	113%-153%
4-Hydroxyatorvastatin acid				
C_{max} (U/mL)	0.25 ± 0.13	0.68 ± 0.40‡	273% (151%-467%)	197%-336%
t_{max} (h)	8 (0.5-34)	9 (0.5-48)	—	
$t_{½}$ (h)	27.7 ± 9.2	21.7 ± 4.4	78% (47%-128%)	64%-101%
AUC(0-72) (U × h/mL)	8.9 ± 4.6	19.3 ± 10.9‡	217% (149%-297%)	182%-256%
AUC(0-∞) (U × h/mL)	11.4 ± 7.9	20.8 ± 11.5‡	182% (138%-282%)	160%-226%
4-Hydroxyatorvastatin lactone				
C_{max} (U/mL)	1.1 ± 0.7	1.4 ± 0.5	134% (48%-359%)	96%-231%
t_{max} (h)	5.5 (1-12)	6 (1.5-10)	—	
$t_{½}$ (h)	24.6 ± 4.2	19.3 ± 4.3‡	78% (61%-101%)	70%-87%
AUC(0-72) (U × h/mL)	23.4 ± 7.7	32.4 ± 9.0‡	139% (102%-181%)	123%-163%
AUC(0-∞) (U × h/mL)	27.3 ± 9.8	35.0 ± 9.9†	128% (101%-168%)	115%-151%

Values are shown as mean ± SD unless otherwise indicated; t_{max} data are given as median and range.
AUC(0-72), Area under plasma concentration–time curve from time 0 to 72 hours.
*$P < .05$.
†$P < .005$.
‡$P < .0005$.

addition, gemfibrozil increased the C_{max} of 2-hydroxyatorvastatin lactone by 36% (range, −41% to 125%; $P = .018$) and that of 4-hydroxyatorvastatin acid by 173% (range, 51% to 367%; $P < .001$) (Table II). However, the $t_{½}$ values of atorvastatin, atorvastatin lactone, 2-hydroxyatorvastatin lactone, and 4-hydroxyatorvastatin lactone were shortened by 13% to 22% by gemfibrozil ($P < .01$).

The lactone/acid AUC ratios of atorvastatin and 4-hydroxyatorvastatin were decreased by about 30% by gemfibrozil ($P < .005$) (Fig 5), reflecting the greater increase in the concentrations of the acid forms caused by gemfibrozil (Table II). The AUC ratios of the 2-hydroxy metabolite and 4-hydroxy metabolite to atorvastatin (acid and lactone) were increased on average by 18% to 54% by gemfibrozil ($P < .005$); that is,

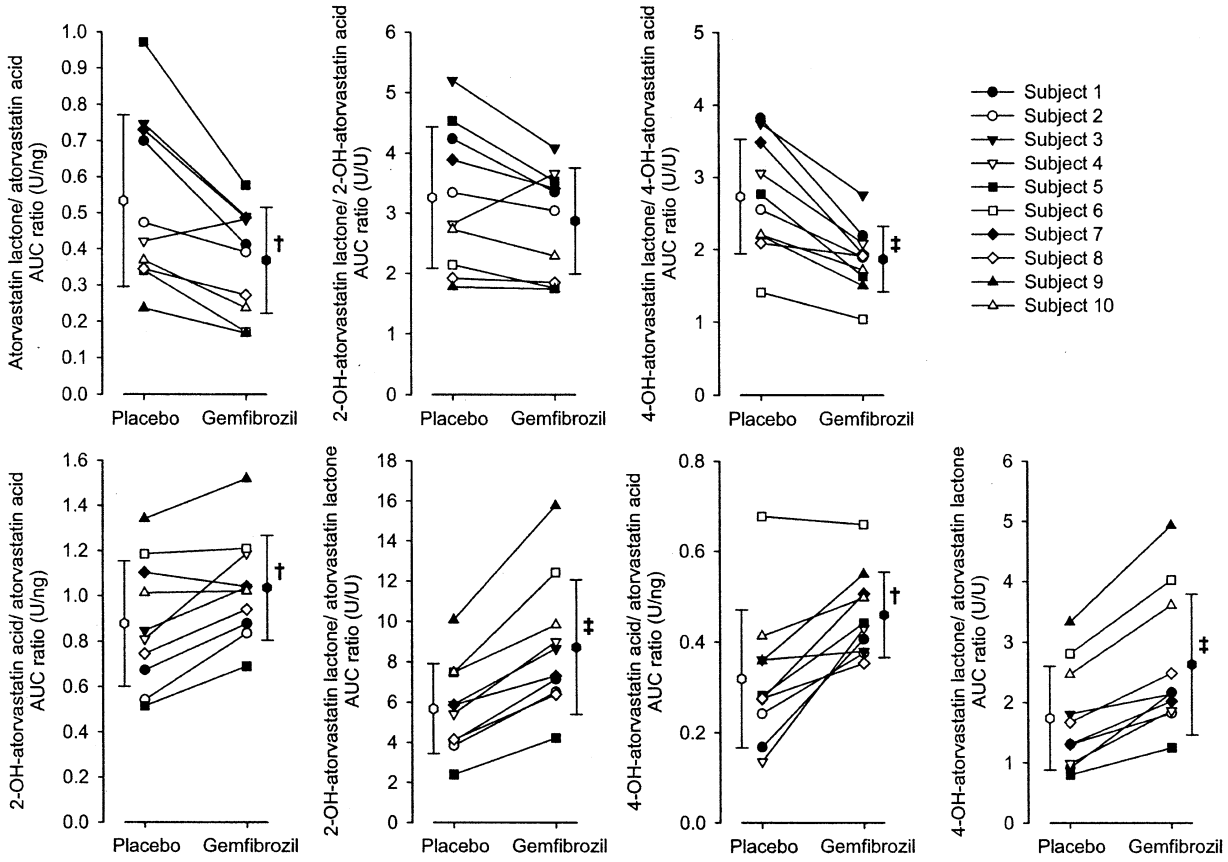

Fig 5. Individual and mean (±SD) AUC ratios of atorvastatin, atorvastatin lactone, 2-hydroxyatorvastatin acid, 2-hydroxyatorvastatin lactone, 4-hydroxyatorvastatin acid, and 4-hydroxyatorvastatin lactone in 10 healthy volunteers after single oral dose of 20 mg atorvastatin on day 3 of 5-day treatment with placebo or 600 mg gemfibrozil twice daily. *Dagger*, $P < .005$; *double dagger*, $P < .0005$.

the AUC values of the hydroxylated metabolites were increased more than those of atorvastatin or its lactone form. The C_{max} and AUC(0-11) of gemfibrozil on day 3 were 30.2 ± 7.4 mg/L and 108 ± 40 mg · h/L, respectively.

DISCUSSION

The results of this work show that rifampin considerably reduces the AUC values (by 43% to 93%) and half-lives of parent atorvastatin (concentrations measured in nanograms per milliliter), and its metabolites (in units per milliliter). There was a considerable intersubject variability in this interaction. For example, the reduction in the AUC of atorvastatin and its active metabolites 2-hydroxyatorvastatin and 4-hydroxyatorvastatin acid ranged from 61% to 88%, 18% to 64%, and 65% to 90%, respectively. On the other hand, gemfibrozil only moderately raised the AUC of atorvastatin (24%) and that of the 2- and 4-hydroxy metabolites (51% and 82% for the active acid forms and almost 30% for the lactones). Interestingly, gemfibrozil also slightly shortened the half-lives of atorvastatin and its lactone metabolites.

Because of the lack of authentic reference standards, the metabolite concentrations are given in arbitrary units relative to the peak height in the chromatogram, which accurately reflect changes in actual plasma concentrations. In previous studies the peak plasma concentrations after 40 mg atorvastatin were about 13 ng/mL for atorvastatin, 4 ng/mL for atorvastatin lactone, 8 to 10 ng/mL for 2-hydroxyatorvastatin acid, 12 to 15 ng/mL for 2-hydroxyatorvastatin lactone, 0.5 ng/mL for 4-hydroxyatorvastatin acid, and 2 ng/mL for 4-hydroxyatorvastatin lactone.[10,11,39] The AUC of

2-hydroxyatorvastatin acid and of 4-hydroxyatorvastatin acid is about 50% to 160% and 10% to 30%, respectively, of that of parent atorvastatin.[10,11,39] In vitro, inhibition of HMG-CoA reductase by the 2- and 4-hydroxylated metabolites is equivalent to that by atorvastatin, and in vivo, about 70% of the HMG-CoA reductase inhibitory activity in plasma has been attributed to active metabolites.[40] Therefore the clinical relevance of the present pharmacokinetic findings is related to the changes in these metabolites in addition to the changes in the parent compound.

Atorvastatin is extensively metabolized via lactonization and CYP3A4-mediated oxidations to 2-hydroxy and 4-hydroxy metabolites (Fig 1),[1,41] and the resulting hydroxylated metabolites are excreted into bile in unchanged form or as glucuronide conjugates.[9,42] In plasma, 2-hydroxyatorvastatin acid and lactone are the dominant metabolites.[1,9-11] In vitro, the intrinsic clearances for the hepatic microsomal CYP-mediated metabolism of atorvastatin lactone to its 2-hydroxy and 4-hydroxy metabolite have been 20- and 83-fold higher, respectively, than those for parent atorvastatin at substrate concentrations below 0.2 mmol/L (less than Michaelis-Menten constant divided by 10).[4] Therefore it has been proposed that the first step in atorvastatin metabolism is lactonization, that atorvastatin lactone is the relevant CYP3A substrate, and that some or most of the open acid metabolites of atorvastatin originate from interconversion of the lactone metabolites.[4]

In this study rifampin greatly increased the AUC ratios of hydroxylated metabolites to atorvastatin (acid or lactone) (Fig 3), consistent with strong induction of the CYP3A4-mediated 2-hydroxylation of atorvastatin and 2- and 4-hydroxylation of atorvastatin lactone. Rifampin increased the C_{max} of the acid forms of the hydroxylated metabolites of atorvastatin more than that of the respective lactone forms, which strongly suggests that rifampin induced the CYP3A4-mediated first-pass metabolism of parent atorvastatin and thereby reduced its concentrations. On the other hand, the AUC ratios of hydroxylated metabolite to atorvastatin were increased more for the lactone forms than for the acid forms (Fig 3). Accordingly, the great reduction in the AUC of atorvastatin lactone by rifampin can be explained by both reduction of its formation (lactonization of atorvastatin is not induced by rifampin, as shown by the reduced lactone/acid ratios) and strong induction of its CYP3A4-mediated further metabolism.[14,15] Nevertheless, although the concentrations of atorvastatin lactone are decreased by rifampin much more than are those of parent atorvastatin, first-pass metabolism of parent atorvastatin by direct CYP3A4-mediated hydroxylation seems to be an important metabolic pathway, at least during treatment with enzyme inducers.

Although induction of CYP3A4 by rifampin is obviously the main mechanism for the reduced concentrations of atorvastatin (acid) and atorvastatin lactone, other mechanisms are also probably involved in the rifampin-atorvastatin interaction. Atorvastatin acid and lactone, as well as many other statins, are substrates for P-glycoprotein.[6,7] Consequently, induction of P-glycoprotein by rifampin[43,44] may have further increased the elimination of atorvastatin and its metabolites (eg, by enhancing their biliary excretion). In particular, this mechanism may explain the accelerated elimination of the hydroxylated metabolites of atorvastatin by rifampin. Rifampin reduced the AUC and elimination $t_{½}$ of 4-hydroxyatorvastatin acid even more than it reduced those of the respective lactone form (Fig 5). Theoretically, induction of the efflux transporter multidrug resistance–associated protein 2 (MRP2), expressed in the intestine and bile canaliculi, by rifampin[45] could have a similar effect on atorvastatin. Moreover, atorvastatin and its metabolites (especially 2-hydroxy metabolites) can undergo glucuronidation,[3,32,33,42] and, therefore, induction of uridine diphosphate–glucuronosyltransferases by rifampin[46,47] could also have contributed to the interaction. Rifampin is an inhibitor of OATP1B1, a liver-specific transporter that mediates uptake of its substrates from blood into hepatocytes.[48,49] However, it seems unlikely that inhibition of this transporter by rifampin would have modulated the interaction, because the last dose of rifampin was taken 17 hours before administration of atorvastatin and rifampin has a short half-life of 2 to 3 hours.

According to our findings, the concentrations of the major active forms of atorvastatin are greatly reduced by rifampin; the AUC values of atorvastatin and 4-hydroxyatorvastatin acid were decreased by about 80% and that of 2-hydroxyatorvastatin was decreased by 43% by rifampin. These changes caused by rifampin are less than those found for simvastatin acid (AUC reduced by 93%)[16] and similar to or somewhat greater than those for fluvastatin (about 50%)[50] but clearly greater than those for pravastatin (31%).[51] In addition, carbamazepine and St John's wort have decreased the AUCs of simvastatin acid by 82% and 52%, respectively,[17,52] but their effects on atorvastatin are not known. In 1 case report, treatment with phenytoin, also an inducer of CYP3A4, was associated with reduced cholesterol-lowering efficacy of atorvastatin and simvastatin despite increased statin doses.[18] Thus the great reduction in the concentrations of atorvastatin and its

active metabolites by rifampin probably necessitates a considerable atorvastatin dose increment in the clinical setting.

Statins with a short half-life are recommended to be given as a single dose in the evening because of the diurnal variation of hepatic cholesterol synthesis, peaking at nighttime.[53] For example, in 2 clinical trials simvastatin (10-40 mg daily), which has a half-life of about 2 to 3 hours, had a better cholesterol-lowering efficacy when taken in the evening than when taken in the morning.[54,55] However, a study with atorvastatin (40 mg daily), whose active forms have a half-life of 10 to 25 hours in the absence of enzyme induction, found no difference in cholesterol concentrations between dosing in the morning and dosing in the evening.[56] In our study the concentrations of atorvastatin and its active metabolites were very low, only about 3% to 22% of control phase values, at 12 hours after dosing during the rifampin phase (Fig 2), as a result of the reduction in their half-lives (to about 2.5-5 hours). Therefore, during treatment with potent inducers of CYP3A4, administration of atorvastatin in the morning may not ensure adequate nighttime drug concentrations for reliable cholesterol-lowering efficacy. Accordingly, dosing of a sufficiently high dose of atorvastatin in the evenings is advisable when it is prescribed to patients treated with enzyme inducers.

In study 2 gemfibrozil increased the concentrations of the hydroxylated metabolites of atorvastatin more than it increased the concentrations of parent atorvastatin (acid), as reflected by the increased metabolite-to-atorvastatin AUC ratios (Fig 5). Moreover, the increase was greater for the acid forms than for the lactone forms; that is, the lactone/acid AUC ratios were decreased by gemfibrozil. These findings differ qualitatively from the effects of CYP3A4 inhibitors on atorvastatin. For example, itraconazole raised the AUC of parent atorvastatin (acid) by about 3-fold and the AUC of atorvastatin lactone by 4-fold, whereas the concentrations of their 2- and 4-hydroxy metabolites were decreased by itraconazole.[10] These findings can have several mechanistic explanations.

Gemfibrozil, which does not inhibit CYP3A4,[27] raises the plasma concentrations of several agents, including cerivastatin, repaglinide, and rosiglitazone, which are metabolized by CYP2C8,[29,57,58] and inhibition of CYP2C8 seems to be a major mechanism of these interactions. For example, gemfibrozil strongly inhibits the formation of the CYP2C8-dependent metabolite of cerivastatin in vivo.[29] In addition, both gemfibrozil and its glucuronide metabolite are relatively potent inhibitors of CYP2C8 in vitro (inhibitory constant [Ki], about 28-75 mmol/L and 4 mmol/L, respectively).[32,34,35] According to in vitro studies, the role of CYP2C8 in the metabolism of atorvastatin is limited.[4] In our study gemfibrozil increased the AUC of atorvastatin (24%) considerably less than it has been shown to increase that of, for example, cerivastatin (5- to 6-fold) or simvastatin acid (2- to 3-fold).[27,29] In addition, gemfibrozil even increased the plasma concentration ratios of 2- and 4-hydroxy metabolite to atorvastatin, ruling out inhibition of the formation of these metabolites by gemfibrozil. This fits well with a limited role of CYP2C8 in the metabolism of atorvastatin and suggests that mechanisms other than inhibition of CYP2C8 are important in the gemfibrozil-atorvastatin interaction.

Inhibition of OATP1B1 by gemfibrozil is probably the most plausible explanation for the findings of study 2. In vitro, gemfibrozil and its glucuronide metabolite inhibit OATP1B1 (50% inhibitory concentration, about 72 mmol/L and 24 mmol/L, respectively) about as potently as they inhibit CYP2C8.[35] Inhibition of OATP1B1 by gemfibrozil can explain, at least partially, its interactions with cerivastatin, as well as with pravastatin and rosuvastatin (the latter 2 statins are excreted largely in unchanged form).[29-31] It is possible that atorvastatin and its metabolites are also substrates for OATP1B1.[7,8] Inhibition of OATP1B1-mediated hepatic uptake of atorvastatin and its hydroxylated metabolites, some of which have probably already been formed during absorption in the intestinal wall, could explain why their plasma concentrations were elevated by gemfibrozil. Moreover, impaired tissue uptake of these compounds, leading to a decreased volume of distribution, might also explain why their half-lives were slightly shortened or remained unchanged by gemfibrozil. Interestingly, cyclosporine (INN, ciclosporin), a potent inhibitor of OATP1B1, has also been shown to raise the concentrations of atorvastatin and its metabolites without having a clear effect on their half-lives.[39,59,60] Another possible explanation for the reduced half-lives could be displacement of atorvastatin (protein binding normally >98%) and its metabolites from plasma proteins by gemfibrozil. In addition, modulation of other metabolic or transport processes by gemfibrozil might contribute to the present interaction findings. For example, gemfibrozil can weakly inhibit the glucuronidation and lactonization of several statin acids, including atorvastatin (50% inhibitory concentration, 316 mmol/L and 63 mmol/L, respectively), in vitro.[32,33] However, although the lactone/acid AUC ratios were decreased by gemfibrozil, inhibition of lactonization is probably not an important explanation for the interaction, because the concentrations of the lac-

tone forms of the 2- and 4-hydroxylated metabolites were also increased by gemfibrozil.

In statin monotherapy, the risk of myopathy has been highest for cerivastatin and much lower for atorvastatin and other statins.[20-22,24-26,61] However, when atorvastatin or another statin is combined with gemfibrozil or fenofibrate, the risk is increased.[20-26,61] In addition, gemfibrozil monotherapy seems to be associated with an increased risk of rhabdomyolysis.[25] In this study gemfibrozil increased the total systemic exposure of atorvastatin and its active acid metabolites on average by 24% to 82%, which is less than that for other statins (between about 100% and 500%),[27-31] except fluvastatin.[62] Thus, although the pharmacokinetic interaction between gemfibrozil and atorvastatin is only moderate, care is warranted, and only relatively low doses of atorvastatin should be used when coadministered with gemfibrozil.

In conclusion, rifampin markedly decreases and gemfibrozil moderately increases the plasma concentrations of atorvastatin and its metabolites. It is advisable to administer atorvastatin in the evening to guarantee adequate concentrations during the nighttime rapid cholesterol synthesis and to increase its dosage when it is coadministered with rifampin or other potent inducers of CYP3A4. Care is warranted, and only low doses of atorvastatin should be used if coadministration with gemfibrozil is required.

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