The effect of gemfibrozil on the pharmacokinetics of rosuvastatin

Background: **Coadministration of statins and gemfibrozil is associated with an increased risk for myopathy, which may be due in part to a pharmacokinetic interaction. Therefore the effect of gemfibrozil on rosuvastatin pharmacokinetics was assessed in healthy volunteers. Rosuvastatin has been shown to be a substrate for the human hepatic uptake transporter organic anion transporter 2 (OATP2). Inhibition of this transporter could increase plasma concentrations of rosuvastatin. The effect of gemfibrozil on rosuvastatin uptake by cells expressing OATP2 was also examined.**

Methods: **In a randomized, double-blind, 2-period crossover trial, 20 healthy volunteers were given oral doses of gemfibrozil, 600 mg, or placebo twice daily for 7 days. On the fourth morning of each dosing period, a single oral dose of rosuvastatin, 80 mg, was coadministered. Plasma concentrations of rosuvastatin, *N*-desmethyl rosuvastatin, and rosuvastatin-lactone were measured. In addition, the effect of gemfibrozil on the uptake of radiolabeled rosuvastatin by OATP2-transfected *Xenopus* oocytes was studied.**

Results: **Gemfibrozil increased the rosuvastatin area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration [AUC(0-t)] 1.88-fold (90% confidence interval, 1.60-2.21) and the maximum observed rosuvastatin plasma concentration (C_{max}) 2.21-fold (90% confidence interval, 1.81-2.69) compared with placebo. *N*-desmethyl rosuvastatin AUC(0-t) and C_{max} decreased by 48% and 39%, respectively. Pharmacokinetics of rosuvastatin-lactone was unchanged. The in vitro results indicate that the maximum gemfibrozil inhibition of rosuvastatin OATP2-mediated uptake was 50%; the inhibition constant for the inhibitory process was 4.0 ± 1.3 μmol/L.**

Conclusions: **Gemfibrozil increased rosuvastatin plasma concentrations approximately 2-fold, which is similar to the effect of gemfibrozil on pravastatin, simvastatin acid, and lovastatin acid plasma concentrations and substantially less than the effect observed for cerivastatin. Gemfibrozil inhibition of OATP2-mediated rosuvastatin hepatic uptake may contribute to the mechanism of the drug-drug interaction. Care is warranted when gemfibrozil is coadministered with rosuvastatin and other statins. (Clin Pharmacol Ther 2004;75: 455-63.)**

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Inhibitors of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase (statins) and fibric acid derivatives such as gemfibrozil may be coprescribed because of their complementary lipid-regulating effects. However, there is increasing evidence that coadministration of statins and gemfibrozil is associated with an increased risk for myopathy and rhabdomyolysis.[1-6] The incidence of rhabdomyolysis is greater with cerivastatin (Baycol and Lipobay; Bayer AG, Leverkusen, Germany) than with other statins.[7,8]

Data from clinical drug interaction trials show that concomitant administration of gemfibrozil with pravastatin,[9] simvastatin,[10] lovastatin,[11] and cerivastatin[12] significantly increases the area under the plasma concentration–time curve and peak plasma concentration of these statins. These results suggest that the increased risk for myopathy may be at least partially related to an increased systemic exposure of the statin resulting from a pharmacokinetic interaction. The mechanism of the

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pharmacokinetic interaction has not been clearly defined, and explanations include gemfibrozil inhibition of statin glucuronidation,[13] cytochrome P450 (CYP) 2C8 metabolism (cerivastatin),[12] or a statin transport protein.[9]

Rosuvastatin (Crestor; licensed from Shionogi and Co Ltd, Osaka, Japan) is a new and highly effective statin that has been developed by AstraZeneca for the treatment of patients with dyslipidemia.[14-16] Metabolic transformation plays a minor role in rosuvastatin clearance in humans (CYP2C9 is the principal CYP isozyme involved in the limited metabolism of rosuvastatin), and thus the potential for metabolically mediated drug-drug interactions is low.[17,18] Ninety percent of an orally administered dose of rosuvastatin is recovered as unchanged drug in the feces.[18]

In humans, the organic anion transporter OATP2 (SLC21A6) (also known as OATP-C) is expressed in the liver and makes a substantial contribution to the hepatic uptake of statins, including pravastatin,[19,20] cerivastatin,[21] and rosuvastatin.[22] Atorvastatin, simvastatin acid, and lovastatin acid are effective inhibitors of pravastatin[19] and rosuvastatin[22] uptake by OATP2 and are also likely to be substrates for this transporter. Gemfibrozil inhibition of OATP2-mediated statin hepatic uptake may explain, at least partly, the drug-drug interactions reported between gemfibrozil and statins.

The aim of this trial was to assess the effect of gemfibrozil on rosuvastatin pharmacokinetics in healthy volunteers. In addition, the effect of gemfibrozil on the uptake of rosuvastatin by OATP2-transfected *Xenopus* oocytes was studied.

METHODS

Human pharmacokinetic trial

Subjects. Subjects were healthy adult volunteers identified from their medical history, physical examination, electrocardiogram (ECG), clinical chemistry, and urinalysis findings. Twenty volunteers entered and completed the trial; all gave written informed consent. Seventeen men and 3 women participated in this study. The mean and SD of age, weight, and height were 41.2 years (6.1 years), 76 kg (9.7 kg), and 172 cm (8 cm), respectively.

Trial design. The trial (AstraZeneca Trial 4522IL/0095) was designed and monitored in accordance with Good Clinical Practice and the Declaration of Helsinki. A local independent ethics committee (Southern Institutional Review Board, Miami, Fla) approved the protocol before the trial started.

The trial was carried out according to a randomized, double-blind, placebo-controlled, 2-period crossover design. Volunteers were given oral doses of gemfibrozil, 600 mg (Lopid; Parke-Davis Inc, Morris Plains, NJ), or placebo (Cebo-Caps; Forest Pharmaceuticals, Inc, St Louis, Mo) twice daily (one capsule given at 8 AM and the other at 8 PM) for 7 days. On the fourth day of each of the 2 dosing periods (days 4 and 15), volunteers were given a single oral dose of rosuvastatin, 80 mg (tablets supplied by AstraZeneca), with the morning dose of gemfibrozil or placebo. Four days separated the last dose of gemfibrozil or placebo during the first dosing period from the start of dosing during the second period; 11 days separated each dose of rosuvastatin.

The trial was conducted at a single center (Clinical Pharmacology Associates, Miami, Fla), and volunteers resided in the center for the duration of the trial. Volunteers fasted for 8 hours before and 4 hours after administration of rosuvastatin on days 4 and 15; identical meals were provided on these days. Volunteers were also required to refrain from strenuous physical exercise, smoking, caffeine-containing drinks and food, alcohol, grapefruit-containing products, and other medications.

Blood sampling. Venous blood samples (7 mL) for rosuvastatin, *N*-desmethyl rosuvastatin, and rosuvastatin-lactone assays were taken before and at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 18, 24, 30, 48, 54, 72, 96, 120, 144, 168, and 192 hours after administration of rosuvastatin on days 4 and 15. Samples were collected into tubes containing lithium-heparin anticoagulant and centrifuged within 30 minutes; plasma was then harvested from the samples. Plasma samples were mixed 1:1 with sodium acetate buffer, 0.1 mol/L (pH 4.0), and stored at −70°C until assay.

Venous blood samples (7.5 mL) for gemfibrozil assay were taken before administration of the morning dose of gemfibrozil or placebo on days 1, 2, and 3 and days 12, 13, and 14. Samples were also taken before and at 0.5, 1, 2, 4, 6, 9, and 12 hours after administration of rosuvastatin on days 4 and 15. Samples were collected into tubes containing sodium-heparin anticoagulant and centrifuged within 30 minutes; plasma was then harvested from the samples and stored at −20°C until assay.

Determination of plasma rosuvastatin, N-desmethyl rosuvastatin, and rosuvastatin-lactone. Plasma samples were analyzed for rosuvastatin, *N*-desmethyl rosuvastatin, and rosuvastatin-lactone by use of a method (HPLC with mass spectrometric detection) developed and validated at AstraZeneca (Wilmington, Del) (unpublished data, 2002). A robotic liquid-handling system was used to perform the sample preparation in a 96-well format. Plasma proteins were precipitated via a

simple protein precipitation and filtration. Analysis of the filtrate was accomplished by multiple-reaction monitoring via positive electrospray ionization–tandem mass spectrometric detection.

The lower limit of quantitation for rosuvastatin was 0.100 ng/mL. The upper limit was 100 ng/mL but was extended by dilution. The lower limit of quantitation for *N*-desmethyl rosuvastatin and rosuvastatin-lactone was 0.250 ng/mL; the upper limit was 25.0 ng/mL.

The accuracy and precision of the analytic method were ensured on the basis of the results for spiked quality control samples, which were assayed on each day of trial sample analysis. For rosuvastatin, accuracy averaged 101% (7.3% relative standard deviation [RSD]) at 0.750 ng/mL, 97.0% (3.9% RSD) at 7.50 ng/mL, and 96.1% (3.4% RSD) at 25.0 ng/mL. For *N*-desmethyl rosuvastatin, accuracy averaged 102% (6.5% RSD) at 0.750 ng/mL, 95.6% (4.1% RSD) at 7.50 ng/mL, and 99.3% (4.1% RSD) at 15.0 ng/mL. For rosuvastatin-lactone, accuracy averaged 97.1% (9.6% RSD) at 0.750 ng/mL, 98.3% (7.7% RSD) at 7.50 ng/mL, and 97.5% (8.2% RSD) at 15.0 ng/mL.

Determination of plasma gemfibrozil. Plasma samples were analyzed for gemfibrozil at PPD Development (Richmond, Va) by a validated method (HPLC with fluorescence detection; LC 56 Version 3). In brief, gemfibrozil and an added internal standard were extracted from human plasma via a liquid-liquid extraction procedure and injected onto an HPLC system with detection via fluorescence excitation.

The lower limit of quantitation for gemfibrozil was 0.0500 μg/mL; the upper limit was 25.0 μg/mL (this was extended by dilution of samples to bring concentrations within the working range of the method). Spiked quality control samples were prepared before the start of sample analysis; accuracy averaged 103% (8.1% RSD) at 0.150 μg/mL, 101% (2.3% RSD) at 1.50 μg/mL, and 94.0% (1.7% RSD) at 15.0 μg/mL.

Pharmacokinetic evaluation. The primary parameters of this trial were area under the rosuvastatin plasma concentration–time curve from time 0 to infinity (AUC) and maximum observed rosuvastatin plasma concentration (C_{max}) after dosing with gemfibrozil compared with placebo. If fewer than 16 volunteers (the number on which the power of the trial was calculated) had AUC data available from both dosing periods, then area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration [AUC(0-t)] was substituted as a primary parameter for all volunteers.

Other pharmacokinetic parameters included the following: time to C_{max} (t_{max}) and terminal elimination half-life (t½) of rosuvastatin; AUC, AUC(0-t), C_{max}, t_{max}, and t½ of *N*-desmethyl rosuvastatin and rosuvastatin-lactone; AUC from 0 to 12 hours [AUC(0-12)] for the gemfibrozil morning dosing interval; C_{max} and t_{max} of gemfibrozil; and observed plasma drug concentration of gemfibrozil before the morning dose on days 2, 3, and 4 and days 13, 14, and 15 (for the assessment of steady state).

AUC was determined as follows: AUC(0-t) + C_{last}/λ_z (in which C_{last} is the last measurable plasma concentration and λ_z is the terminal elimination rate constant calculated by log-linear regression of the terminal portion of the plasma concentration–time curve when there were sufficient data). AUC(0-t) and AUC(0-12) were determined by use of the linear trapezoidal rule. C_{max} and t_{max} were determined by visual inspection of the plasma concentration–time curves; t½ was calculated as $0.693/\lambda_z$.

Statistical methods. A trial including 16 volunteers would have had greater than 80% power for rosuvastatin AUC [or AUC(0-t)] and 80% power for rosuvastatin C_{max} to ensure that the 90% confidence interval (CI) for the treatment effect (ratio of gemfibrozil plus rosuvastatin-placebo plus rosuvastatin geometric least-square means [glsmeans]) would be contained within the interval of 0.7 to 1.43, with the assumption that the true underlying ratio was 1.[23]

Rosuvastatin AUC [or AUC(0-t)] and C_{max} were log-transformed before analysis. The parameters were then analyzed by an ANOVA model, which included the effects of sequence, period, and treatment (gemfibrozil or placebo), as well as volunteer within sequence as a random effect. The results of the analysis are presented in terms of the treatment effect and its 90% CI. This statistical analysis was also performed on the *N*-desmethyl rosuvastatin and rosuvastatin-lactone data.

Rosuvastatin (untransformed) t½ was also analyzed as described. The results of the analysis are presented in terms of the treatment effect (difference of gemfibrozil plus rosuvastatin minus placebo plus rosuvastatin least square means [lsmeans]) and its 95% CI.

Tolerability. The following assessments were performed: adverse event reports, medical examinations, clinical laboratory data, and ECGs.

In vitro study

Materials. Tritium-labeled rosuvastatin was supplied by AstraZeneca (Macclesfield, United Kingdom). Collagenase (type A) was supplied by Roche Molecular Biochemicals (Mannheim, Germany). All other chem-

icals were supplied by Sigma Chemical Company (St Louis, Mo).

Xenopus oocytes. Stage V to VI morphologically healthy oocytes from *Xenopus laevis* were obtained from the South African Xenopus Facility (Knysna, Republic of South Africa).

Study design. Uptake of [^{3}H]rosuvastatin into oocytes expressing OATP2 and into water-injected control oocytes was measured over a range of rosuvastatin concentrations (0-100 μmol/L). Uptake of [^{3}H]rosuvastatin (5 μmol/L) into oocytes expressing OATP2 was also measured in the presence of a range of gemfibrozil concentrations (0-50 μmol/L).

Synthesis of complementary ribonucleic acid. Human *OATP2*1a* complementary deoxyribonucleic acid (cDNA) was used as a template for cDNA synthesis. Plasmids were linearized with a single restriction digest upstream of the T7 promoter. In vitro transcription of the linear cDNA template was achieved with the mMessage mMachine T7 Kit (Ambion, Huntingdon, United Kingdom).

Preparation of oocytes. Oocytes were treated with collagenase for 1 to 2 hours at 20°C until the follicular layer had been removed. After overnight storage at 18°C in 1-mmol/L Barth's solution, oocytes were injected with either complementary ribonucleic acid (cRNA) (20 ng) or water (50 nL). The oocytes were allowed 2 to 3 days to translate the cRNA and express the protein at the plasma membrane.

Assessment of rosuvastatin uptake by oocytes. Ten oocytes per experimental condition were incubated in Barth's solution containing either rosuvastatin (0-100 μmol/L) or rosuvastatin (5 μmol/L) plus gemfibrozil (0-50 μmol/L). Each uptake solution contained [^{3}H]rosuvastatin at 3 μCi/mL. After incubation at 18°C for 1 hour, the oocytes were washed. Individual oocytes were placed into vials containing 500 μL of 2% sodium dodecyl sulfate and allowed to lyse. The ^{3}H content was then measured by scintillation spectrophotometry.

Statistical methods. Results are expressed as mean ± SEM. The model used to relate the rate of uptake to rosuvastatin concentration in the media was as follows:

$$V_0 = (V_{max} \cdot S)/(K_a + S)$$

where V_0 is the rate of uptake (in picomoles per oocyte per hour), V_{max} is the maximum rate of uptake (in picomoles per oocyte per hour), K_a is the association constant, and S is the rosuvastatin concentration in the media (in micromoles per liter). Curve fitting and determination of K_a and inhibition constant (IC_{50}) values were achieved by nonlinear regression analysis (Levenberg-Marquardt). All curve fitting and rate constant determinations were performed after subtraction of rosuvastatin uptake into water-injected oocytes from the total uptake measured in cRNA-injected oocytes.

RESULTS

Human pharmacokinetic trial

Rosuvastatin pharmacokinetic parameters. The geometric mean plasma concentrations of rosuvastatin over time and summary pharmacokinetic parameters of rosuvastatin are presented in Fig 1 and Table I, respectively.

Because AUC data from both dosing periods were available for only 11 volunteers (it was not possible to determine a reliable AUC in the other volunteers), AUC(0-t) was substituted as a primary parameter and subjected to statistical analysis. AUC(0-t) was considered to be a suitable replacement for AUC in the assessment of exposure because it represented a high proportion (typically >95%) of AUC in those volunteers for whom it was possible to determine a reliable AUC.

The statistical comparison of the primary parameters is presented in Table I. After coadministration with gemfibrozil, rosuvastatin glsmean AUC(0-t) was increased 1.88-fold and glsmean C_{max} was increased 2.21-fold compared with placebo. Individual treatment effects ranged from 0.909 to 3.76 for AUC(0-t) and from 0.843 to 5.60 for C_{max}.

No significant difference in rosuvastatin t½ was observed between the gemfibrozil and placebo treatments (Table I).

N-desmethyl rosuvastatin pharmacokinetic parameters. The geometric mean plasma concentrations of *N*-desmethyl rosuvastatin over time and summary pharmacokinetic parameters of *N*-desmethyl rosuvastatin are presented in Fig 1 and Table I, respectively. A 48% reduction in glsmean AUC(0-t) and a 39% reduction in glsmean C_{max} were noted when rosuvastatin was coadministered with gemfibrozil compared with placebo.

Rosuvastatin-lactone pharmacokinetic parameters. The geometric mean plasma concentrations of rosuvastatin-lactone over time and summary pharmacokinetic parameters of rosuvastatin-lactone are presented in Fig 1 and Table I, respectively. No significant difference was observed in rosuvastatin-lactone glsmean AUC(0-t) and C_{max} between the gemfibrozil and placebo treatments.

Gemfibrozil pharmacokinetic parameters. Gemfibrozil geometric mean (gmean) AUC(0-12) was 98.9 μg · h/mL (22.2%) and C_{max} was 25.6 μg/mL (percent coefficient of variation, 34.4%); the median t_{max} was 1.5 hours (range, 0.5-4.0 hours). The gemfibrozil expo-

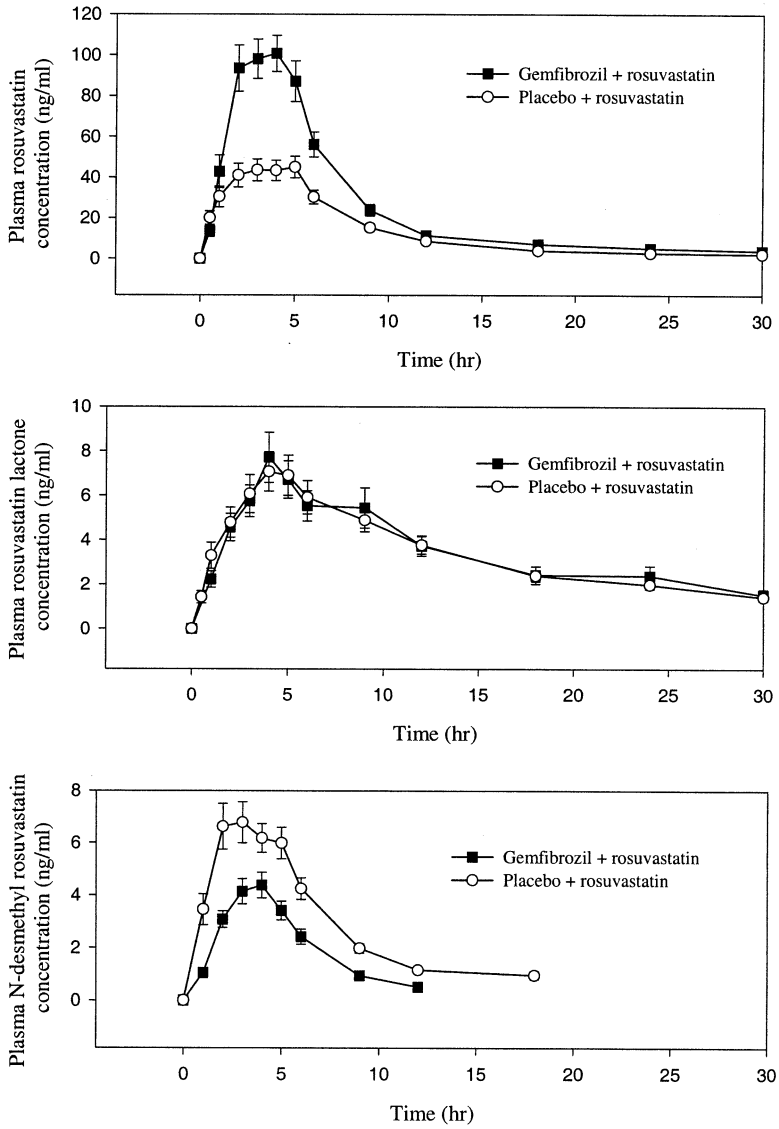

Fig 1. Plasma concentrations of rosuvastatin and metabolites over time in 20 healthy volunteers after administration of a single dose of rosuvastatin, 80 mg, on day 4 during treatment with gemfibrozil, 600 mg, or placebo twice daily for 7 days.

sures observed in this trial are consistent with those observed in other studies.[10,24]

The gmean trough plasma concentrations of gemfibrozil on days 2, 3, and 4 were as follows: 1.2 μg/mL (percent coefficient of variation, 46.9%), 1.5 μg/mL (percent coefficient of variation, 42.6%), and 1.4 μg/mL (percent coefficient of variation, 46.2%), respectively. These values indicate that gemfibrozil was at steady state when rosuvastatin was administered.

Tolerability. Three volunteers had asymptomatic increases in ALT level (<2.5× upper limit of normal) during treatment with gemfibrozil plus rosuvastatin. These elevations were not observed during treatment with placebo plus rosuvastatin and resolved after discontinuation of gemfibrozil.

In vitro study

The uptake of [^{3}H]rosuvastatin into oocytes expressing OATP2 is shown in Fig 2. The data show that rosuvastatin is a high-affinity substrate for OATP2. At each concentration assessed, the uptake of rosuvastatin into oocytes expressing OATP2 was approximately 10-

Table I. Summary pharmacokinetic parameters of rosuvastatin, rosuvastatin-lactone, and *N*-desmethyl rosuvastatin in 20 healthy volunteers after administration of rosuvastatin, 80 mg, after pretreatment with gemfibrozil, 600 mg, or placebo twice daily for 7 days

Rosuvastatin or metabolite parameter	*Summary statistic*	*Gemfibrozil + rosuvastatin (N = 20)*	*Placebo + rosuvastatin (N = 20)*	*Treatment effect**	*90% CI*	*P value*
Rosuvastatin						
AUC(0-t) (ng · h/mL)	gmean and % CV	771 (48.8)	410 (47.7)	1.88	1.60 to 2.21	<.0001
C_{max} (ng/mL)	gmean and % CV	109 (42.9)	49.5 (47.6)	2.21	1.81 to 2.69	<.0001
t_{max} (h)	Median and range	3.0 (2.0-5.0)	4.0 (0.5-5.0)	NA	NA	NA
t½ (h)	Mean and SD	23.3 (17.7)†	17.1 (6.3)‡	3.53	–2.19 to 9.26 –1.11 to 8.17§	.196
N-desmethyl rosuvastatin						
AUC(0-t) (ng · h/mL)	gmean and % CV	26.3 (55.6)	50.2 (54.7)	0.52	0.42 to 0.65	<.0001
C_{max} (ng/mL)	gmean and % CV	4.4 (41.1)	7.2 (46.6)	0.61	0.51 to 0.74	.0003
t_{max} (h)	Median and range	4.0 (2.0-5.0)	3.0 (2.0-5.0)	NA	NA	NA
t½ (h)	Mean and SD	4.1 (3.3)‖	4.7 (2.7)¶	NA	NA	NA
Rosuvastatin-lactone						
AUC(0-t) (ng · h/mL)	gmean and % CV	114 (81.8)	110 (55.2)	1.04	0.86 to 1.25	.722
C_{max} (ng/mL)	gmean and % CV	6.9 (69.0)	7.1 (53.6)	0.97	0.80 to 1.19	.8190
t_{max} (h)	Median and range	4.0 (3.0-30.0)	4.5 (2.0-18.0)	NA	NA	NA
t½ (h)	Mean and SD	30.0 (21.2)#	20.5 (13.3)**	NA	NA	NA

CI, Confidence interval; AUC(0-t), area under plasma concentration–time curve from time 0 to time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; t_{max}, time to C_{max}; t½, terminal elimination half-life; gmean, geometric mean; % CV, coefficient of variation expressed as percentage of geometric mean; NA, not applicable.

*Ratio of gemfibrozil + rosuvastatin/placebo + rosuvastatin geometric least-square means for AUC(0-t) and C_{max} and difference of gemfibrozil + rosuvastatin minus placebo + rosuvastatin least-square means for t½.

†n = 16.

‡n = 14.

§95% CI.

‖n = 8.

¶n = 5.

#n = 6.

**n = 10.

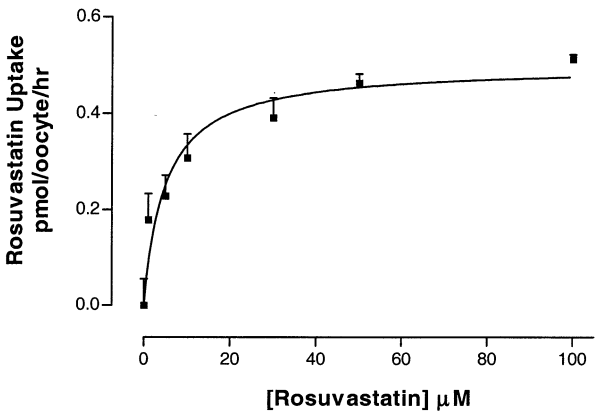

Fig 2. Uptake of [^{3}H]rosuvastatin into oocytes expressing the organic anion transporter OATP2 (SLC21A6) (also known as OATP-C). Nonlinear least-squares regression analysis of the data from 8 independent experiments yielded an apparent association constant (K_a) of 8.5 ± 1.1 μmol/L. (Each data point represents the mean ± SEM of [^{3}H]rosuvastatin uptake into 10 oocytes from a single animal.)

fold greater than the uptake into water-injected control oocytes. Nonlinear least-squares regression analysis of the OATP-C–mediated component of rosuvastatin uptake yielded an apparent K_a of 8.5 ± 1.1 μmol/L.

The effect of gemfibrozil on the kinetics of OATP-C–mediated [^{3}H]rosuvastatin uptake is shown in Fig 3. The maximum inhibition of rosuvastatin uptake by gemfibrozil was 50%. The IC_{50} for the inhibitory process was 4.0 ± 1.3 μmol/L.

DISCUSSION

In this trial, administration of the usual therapeutic dose of gemfibrozil increased the systemic exposure of rosuvastatin approximately 2-fold, decreased *N*-desmethyl rosuvastatin AUC(0-t) by 48% and C_{max} by 39%, and had no effect on plasma rosuvastatin-lactone concentrations. No change in rosuvastatin t½ was observed. The changes in rosuvastatin AUC(0-t) are similar to those reported for pravastatin,[9] simvastatin acid,[10] and lovastatin acid[11] (ie, approximately

2-fold) but are substantially less than those reported for cerivastatin[12] (5.6-fold).

Rosuvastatin has been shown to be a high-affinity substrate for the liver-specific OATP2 influx transporter known to be present in the basolateral membrane of human hepatocytes.[22] Pravastatin has also been identified as a substrate for this transporter.[19] Simvastatin acid, atorvastatin, and lovastatin acid are effective inhibitors of pravastatin and rosuvastatin transport.[19,22] Thus in vivo inhibition of OATP2 could lead to increased plasma concentrations of statins. These in vitro results indicate that gemfibrozil inhibits OATP2-mediated rosuvastatin uptake in *Xenopus* oocytes. It is of interest that the maximal inhibition produced by gemfibrozil was only 50% of the maximal uptake in vitro. However, the mean total gemfibrozil plasma concentration at C_{max} was 102 μmol/L, and the estimated free fraction was approximately 5 μmol/L. The free fraction value is similar to the IC_{50} value for gemfibrozil. Inhibition of this transport process by gemfibrozil likely contributes to the drug interaction between gemfibrozil and rosuvastatin or other statins. Gemfibrozil inhibition of other statin transporters could also contribute to the drug-drug interaction. Pravastatin has been shown to be a substrate for the multidrug resistance protein MRP2 located in hepatocyte canalicular membranes.[25] Inhibition of this transporter by gemfibrozil could elevate pravastatin plasma concentrations. It is unknown whether rosuvastatin is a substrate for this transporter or whether gemfibrozil is an inhibitor of this transporter. MRPs also occur in the gut wall, and it has been suggested that they contribute to the low bioavailability of statins.[26] The absolute bioavailability of rosuvastatin is 20%. Inhibition of MRP rosuvastatin efflux at the intestine by gemfibrozil could increase the bioavailability of rosuvastatin, resulting in higher plasma concentrations. The contribution of this mechanism to the drug interaction is also unknown.

Gemfibrozil could have an effect on other metabolic processes that may contribute to the mechanism of the statin interactions. Prueksaritanont et al[13] have demonstrated the glucuronidation of simvastatin acid in dogs and have shown that gemfibrozil inhibits formation of the glucuronide conjugate. Studies with human liver microsomes have shown the formation of acyl glucuronide conjugates of simvastatin acid, atorvastatin acid, cerivastatin acid, and rosuvastatin acid.[27,28] Studies with human hepatocytes in culture have demonstrated that gemfibrozil can inhibit the glucuronidation of simvastatin acid, atorvastatin acid, cerivastatin acid, and rosuvastatin acid.[28] The results of these studies suggest that inhibition of statin glucuronidation may contribute

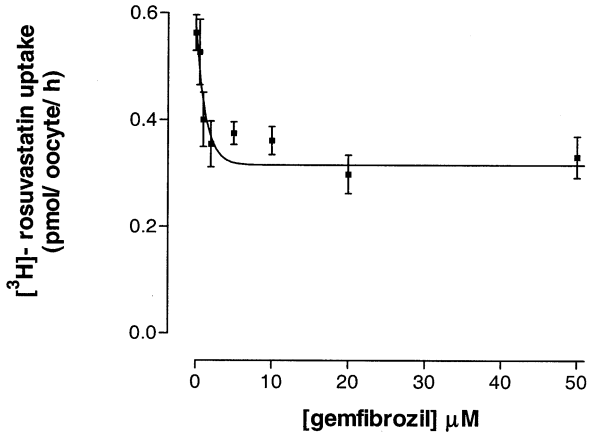

Fig 3. Effect of gemfibrozil on kinetics of OATP-C–mediated [^{3}H]rosuvastatin uptake. The inhibition constant (IC_{50}) for the gemfibrozil inhibitory process was 4.0 ± 1.3 μmol/L. (Each data point represents the mean ± SEM of 8 to 10 oocytes from a single experiment representative of the data from 4 independent experiments.)

to the mechanism by which gemfibrozil increases statin plasma concentrations. A glucuronide conjugate of rosuvastatin acid has not been identified in humans.[18] This might reflect the instability of statin glucuronide conjugates and their spontaneous conversion to the corresponding lactone form, particularly at pH values greater than 7.[27]

When the effect of fenofibrate on the pharmacokinetic properties of rosuvastatin was studied, the plasma concentrations of rosuvastatin were found to be similar in the presence and absence of fenofibrate.[29] In addition, bezafibrate was found not to affect lovastatin plasma concentrations.[11] Thus not all fibrates demonstrate a pharmacokinetic interaction with statins.

Gemfibrozil is also an inhibitor of CYP2C8,[30] and CYP2C8 is a major contributor to cerivastatin clearance.[12] Inhibition of cerivastatin hepatic uptake by OATP2, glucuronide formation, and oxidative metabolism may be the reason why cerivastatin shows the greatest interaction with gemfibrozil.

In this trial gemfibrozil produced modest but significant reductions in *N*-desmethyl rosuvastatin plasma concentrations. The *N*-desmethyl metabolite is formed primarily by CYP2C9,[17] and gemfibrozil is a potent inhibitor of CYP2C9.[31] The reductions in *N*-desmethyl rosuvastatin plasma concentrations could reflect inhibition of rosuvastatin CYP2C9 metabolism by gemfibrozil. However, this cannot be the mechanism by which gemfibrozil increases rosuvastatin plasma concentrations, because oxidative metabolism contributes little to

rosuvastatin disposition.[17,18] This conclusion is strongly supported by the results of a rosuvastatin-drug interaction trial in which healthy volunteers were given rosuvastatin with the potent CYP2C9 inhibitor fluconazole: Fluconazole did not produce a clinically relevant increase in rosuvastatin plasma concentrations.[32]

In summary, gemfibrozil inhibition of OATP2-mediated rosuvastatin hepatic uptake is likely a major contributor to the mechanism of the drug-drug interaction. Care is warranted when coadministering gemfibrozil with rosuvastatin and other statins.

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