Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of glimepiride

Objective: Our objective was to study the effects of gemfibrozil on the pharmacokinetics and pharmacodynamics of glimepiride, a new sulfonylurea antidiabetic drug and a substrate of cytochrome P4502C9 (CYP2C9).

Methods: In a randomized, 2-phase crossover study, 10 healthy volunteers were treated for 2 days with 600 mg oral gemfibrozil or placebo twice daily. On day 3, they received a single dose of 600 mg gemfibrozil or placebo and 1 hour later a single dose of 0.5 mg glimepiride orally. Plasma glimepiride, serum insulin, and blood glucose concentrations were measured up to 12 hours.

Results: Gemfibrozil increased the mean total area under the plasma concentration-time curve of glimepiride by 23% (range, 6%-56%; $P < .005$). The mean elimination half-life of glimepiride was prolonged from 2.1 to 2.3 hours ($P < .05$) by gemfibrozil. No statistically significant differences were found in the serum insulin or blood glucose variables between the two phases.

Conclusions: Gemfibrozil modestly increases the plasma concentrations of glimepiride. This may be caused by inhibition of CYP2C9. (Clin Pharmacol Ther 2001;70:439-45.)

Mikko Niemi, MD, Pertti J. Neuvonen, MD, and Kari T. Kivistö, MD
Helsinki, Finland

The sulfonylurea glimepiride is widely used in the treatment of non–insulin-dependent diabetes mellitus. Glimepiride is almost completely bioavailable from the gastrointestinal tract and, according to the manufacturer, the cytochrome P450 (CYP) 2C9 enzyme is involved in its biotransformation.[1] Fluconazole, an inhibitor of CYP2C9[2,3] and some other CYP enzymes, increased the area under the concentration-time curve (AUC) of glimepiride by about 140%.[4]

Case reports have suggested that fibrate drugs, including gemfibrozil, may increase the effects of sulfonylureas and warfarin.[5-8] A possible explanation for these interactions could be inhibition of the CYP2C9-mediated metabolism of these drugs by fibrates. However, there are few controlled studies on the effects of fibrates on the pharmacokinetics of CYP2C9 substrates. The aim of this study was to investigate the effects of gemfibrozil on the pharmacokinetics and pharmacodynamics of the CYP2C9 substrate glimepiride.

From the Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital.

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Reprint requests: Kari T. Kivistö, MD, Department of Clinical Pharmacology, Helsinki University Central Hospital, PO Box 340, FIN-00029 HUS, Finland.

E-mail: *kari.kivisto@hus.fi*

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MATERIALS AND METHODS

Subjects. Ten healthy volunteers (2 men and 8 women; age range, 20-26 years; weight range, 52-78 kg) participated in the study after they had given written informed consent (Table I). The volunteers were ascertained to be healthy by medical history, physical examination, and routine laboratory tests (including fasting serum glucose) before they were entered in the study. All 8 female subjects were using oral contraceptive steroids. One of the subjects was a tobacco smoker.

Study design. The study protocol was approved by the Ethics Committee for Studies in Healthy Subjects of the Hospital District of Helsinki and Uusimaa and the Finnish National Agency for Medicines. A random-

Table I. Characteristics of subjects

Subject No.	*Sex*	*Age (y)*	*Weight (kg)*	*Smoker*	*Use of oral contraceptives*	*Gemfibrozil C_{max} (mg/L)*	*Gemfibrozil AUC (1-13) (mg · h/L)*
1	Female	22	55	No	0.15 mg desogestrel plus 20 μg ethinyl estradiol (INN, ethinylestradiol)	25.9	84.4
2	Female	25	75	No	2 mg cyproterone acetate (INN, cyproterone) plus 35 μg ethinyl estradiol	15.6	52.8
3	Male	22	78	No	No	25.1	66.6
4	Female	21	56	No	75 μg gestodene plus 20 μg ethinyl estradiol	14.3	62.9
5	Female	20	55	No	0.15 mg desogestrel plus 30 μg ethinyl estradiol	23.5	104.8
6	Male	23	74	No	No	29.1	87.2
7	Female	24	52	No	75 μg gestodene plus 30 μg ethinyl estradiol	33.8	69.9
8	Female	22	69	No	0.15 mg desogestrel plus 20 μg ethinyl estradiol	12.0	42.3
9	Female	26	64	No	0.15 mg desogestrel plus 20 μg ethinyl estradiol	18.9	63.5
10	Female	25	68	Yes	50 μg gestodene plus 30 μg ethinyl estradiol (6 tablets); 70 μg gestodene plus 40 μg ethinyl estradiol (5 tablets); 100 μg gestodene plus 30 μg ethinyl estradiol (10 tablets)	31.7	58.1
Mean ± SD		23.0 ± 1.9	64.6 ± 9.6			23.0 ± 7.5	69.3 ± 18.3

ized, 2-phase crossover study with a washout period of 2 weeks was carried out. The volunteers received 600 mg gemfibrozil (one Lopid 600 mg tablet; Gödecke/Parke Davis, Freiburg, Germany) or placebo twice daily for 2 days. On day 3, after an overnight fast, they received 600 mg gemfibrozil or placebo at 8 AM. At 9 AM, a single oral dose of 0.5 mg glimepiride (one half of an Amaryl 1 mg tablet; Hoechst Marion Roussel, Stockholm, Sweden) was administered with 150 ml water. The volunteers ingested glimepiride while they were seated and they remained seated for the next 3 hours. A standard light breakfast was served precisely 15 minutes after the administration of glimepiride, a standard warm meal was served after 3 hours, and a standard light meal was served after 7 hours. The breakfast was eaten within 10 minutes and contained approximately 370 kcal energy, 70 g carbohydrates, 8 g protein, and 6 g fat. Food intake was identical during both days of glimepiride administration. The subjects were under direct medical supervision during the days of administration of glimepiride, and blood glucose concentrations were measured throughout the day. Glucose for intravenous use and glucagon for intramuscular use were available in case of severe hypoglycemia, but they were not needed.

Blood sampling and determination of blood glucose and serum insulin concentrations. On the days of administration of glimepiride, a forearm vein of each subject was cannulated with a plastic cannula and kept patent with an obturator. Timed blood samples were drawn before the administration of glimepiride and ½, 1, 1½, 2, 2½, 3, 4, 5, 7, 9, and 12 hours later. The blood samples were taken into two tubes—a 5-ml tube with an inert gel barrier for serum samples and a 10-ml tube containing ethylenediaminetetraacetic acid (EDTA) for plasma samples. The serum tubes were placed onto ice, and serum was separated immediately after blood sampling. Blood glucose concentrations were measured immediately after each blood sampling in the EDTA-samples by the glucose oxidase method with the Precision G Blood Glucose Testing System (Medisense, Bedford, Mass). Plasma was separated within 30 minutes after the determination of blood glucose, and the samples were stored at −40°C until analysis. The between-day coefficient of variation (CV) for blood glucose was 3.8% at 3.0 mmol/L, 8.4% at 5.4 mmol/L,

Table II. Pharmacokinetic variables of 0.5 mg glimepiride in 10 healthy volunteers after 5 doses of placebo or 600 mg gemfibrozil administered twice daily

Variable	*Placebo phase (control)*	*Gemfibrozil phase*
C_{max} (ng/ml)	31.3 ± 5.2	35.6 ± 13.6
% of control (range)	100%	114% (79%-165%)
t_{max} (h)	1.5 (1-4)	1.5 (1-3)
$t_{½}$ (h)	2.1 ± 0.6	2.3 ± 0.5*
% of control (range)	100%	108% (93%-143%)
AUC(0-12) (ng · h/ml)	130.2 ± 57.4	161.4 ± 71.5†
% of control (range)	100%	124% (106%-157%)
AUC(0-∞) (ng · h/ml)	137.9 ± 69.2	169.9 ± 82.7†
% of control (range)	100%	123% (106%-156%)

Data are mean values ± SD; t_{max} data are given as median with range.
*$P < .05$, versus control.
†$P < .005$, versus control.

Table III. Pharmacodynamic variables of 0.5 mg glimepiride in 10 healthy volunteers after 5 doses of placebo or 600 mg gemfibrozil administered twice daily

Variable	*Placebo phase (control)*	*Gemfibrozil phase*
Serum insulin		
Incremental AUC(0-3) (mU · h/L)	63.6 ± 30.3	68.8 ± 50.5
% of control (range)	100%	108% (37%-203%)
Incremental AUC(0-7) (mU · h/L)	160.7 ± 102.3	146.7 ± 109.0
% of control (range)	100%	91% (49%-206%)
Maximum increase (mU/L)	49.9 ± 29.1	50.2 ± 35.9
% of control (range)	100%	101% (40%-184%)
Blood glucose		
Decremental AUC(0-3) (mmol · h/L)	−0.88 ± 1.27	−1.05 ± 2.13
Decremental AUC(0-7) (mmol · h/L)	−1.96 ± 3.65	−1.50 ± 3.70
Maximum increase (mmol/L)	2.1 ± 0.7	1.8 ± 1.0
Maximum decrease (mmol/L)	1.0 ± 1.0	0.9 ± 0.8

Data are mean values ± SD.

and 2.5% at 16.8 mmol/L (n = 4). Serum insulin concentrations were measured by a fluoroimmunoassay method with a commercially available kit, Auto-DELFIA Insulin (Wallac Oy, Turku, Finland). The interassay CV for the kit with a full standard curve was 2.3% at 5.7 mU/L, 3.0% at 13.7 mU/L, and 3.5% at 30.2 mU/L.[9]

Determination of plasma drug concentrations. Plasma glimepiride concentrations were quantified by liquid chromatography–tandem mass spectrometry with use of the Perkin-Elmer SCIEX API 3000 LC/MS/MS System (Sciex Division of MDS Inc, Toronto, Ontario, Canada), with glyburide (INN, glibenclamide) as the internal standard. A Hypersil BDS-C_{18} column (Hewlett-Packard, Waldbronn, Germany) and a mobile phase consisting of acetonitrile (57%) and 10-mmol/L ammonium formate (pH 3.5; 43%) were used. The ion transitions monitored were mass-to-charge ratio of 491 to 352 for glimepiride and mass-to-charge ratio of 494 to 369 for glyburide. These transitions represent the product ions of the $[M + H]^+$ ions. The limit of quantification of the method was 0.05 ng/ml, and the between-day coefficient of variation (CV) was 6.9% at 0.1 ng/ml, 2.3% at 0.5 ng/ml, 2.7% at 5.0 ng/ml, and 4.6% at 50.0 ng/ml (n = 5). Plasma gemfibrozil concentrations were determined by HPLC with ultraviolet detection,[10] with ibuprofen used as the internal standard. The limit of quantification was 0.1 mg/L, and the between-day CV was 9.7% at 2.1 mg/L, 6.8% at 14.6 mg/L, and 2.6% at 29.6 mg/L (n = 6).

Pharmacokinetics. The pharmacokinetic characteristics of glimepiride were characterized by peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), area under the concentration-time curve [AUC(0-12) and AUC(0-∞)], and elimination half-life ($t_{½}$). The terminal log-linear part of the concentration-time curve was

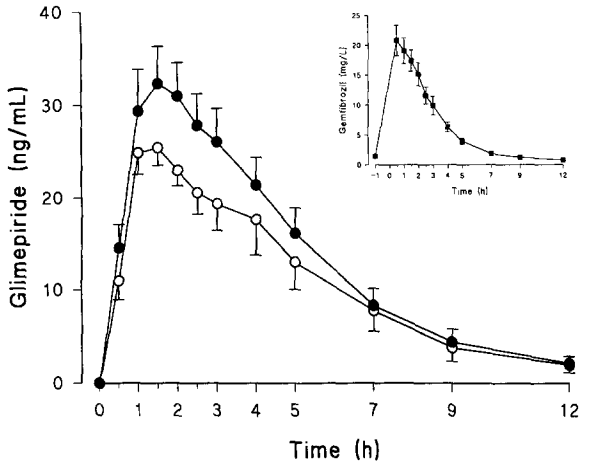

Fig 1. Mean ± SEM plasma concentrations of glimepiride in 10 healthy volunteers after a single oral dose of 0.5 mg glimepiride after 5 doses of placebo or 600 mg gemfibrozil administered twice daily. *Open circles,* Glimepiride during placebo; *solid circles,* glimepiride during gemfibrozil. *Inset* depicts mean ± SEM plasma concentrations of gemfibrozil on day of administration of glimepiride. Time zero refers to administration of glimepiride (ie, 1 hour after last dose of gemfibrozil).

identified visually for each subject. The elimination rate constant (k_e) was determined by linear regression analysis of the log-linear part of the plasma drug concentration-time curve. The $t_{½}$ was calculated by the equation $t_{½} = \ln 2/k_e$. The AUC values were calculated by use of the linear trapezoidal rule for the rising phase of the plasma drug concentration-time curve 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 pharmacokinetic parameters of gemfibrozil were characterized by C_{max} and AUC(1-13), that is, the AUC from 1 hour after the last dose of gemfibrozil up to 13 hours.

Pharmacodynamics. The pharmacodynamic characteristics of glimepiride were characterized by the serum insulin and blood glucose responses. The serum insulin response was characterized by determining the incremental area under the serum insulin concentration-time curve from 0 to 3 hours [AUC(0-3)] and from 0 to 7 hours [AUC(0-7)] and the maximum increase in the serum insulin concentration during the first 3 hours after the administration of glimepiride compared with the baseline value (before glimepiride administration). The blood glucose response to glimepiride was characterized by determining the decremental area under

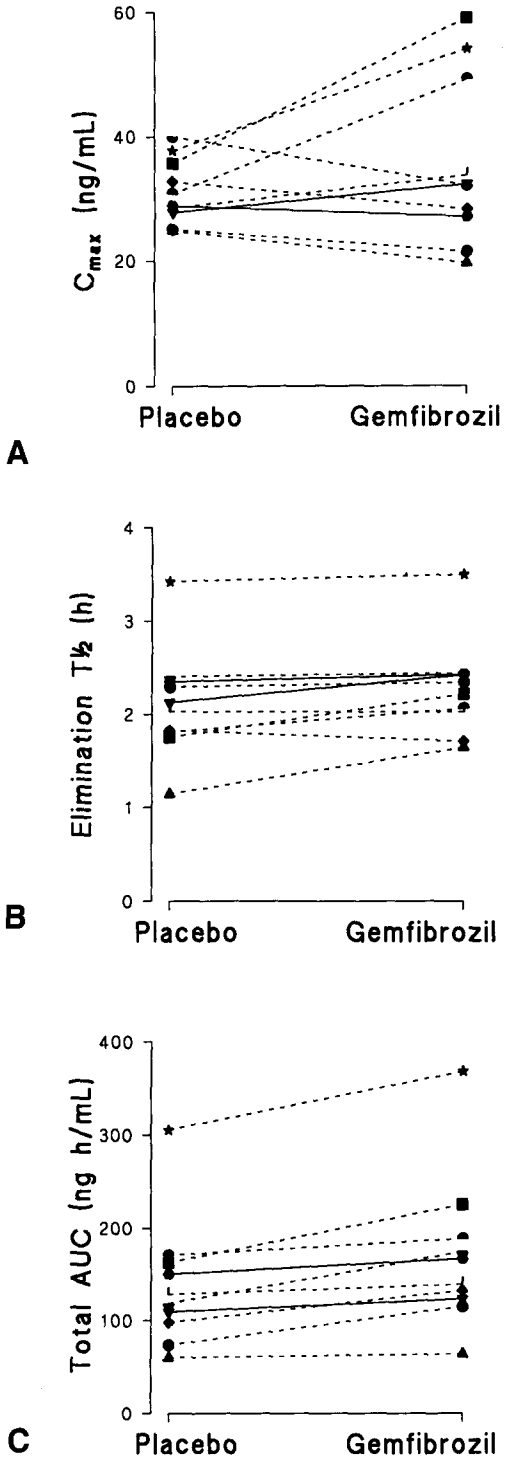

Fig 2. Individual peak plasma concentration (C_{max}) (**A**), elimination half-life ($t_{½}$) (**B**), and total area under the concentration-time curve [AUC(0-∞)] (**C**) values of glimepiride in 10 healthy volunteers after a single oral dose of 0.5 mg glimepiride after 5 doses of placebo or 600 mg gemfibrozil administered twice daily. *Broken lines,* Subjects who were using oral contraceptive steroids.

the blood glucose concentration-time curve from 0 to 3 hours [AUC(0-3)] and from 0 to 7 hours [AUC(0-7)], as well as the maximum increase and the maximum decrease in the blood glucose concentration from the baseline value during the first 3 hours after the administration of glimepiride. The AUC values were calculated by the linear trapezoidal rule.

Statistical analysis. Results are expressed as mean values ± standard deviation (SD) in the text and tables and, for clarity, as mean values ± standard error of the mean (SEM) in the figures. The pharmacokinetic and pharmacodynamic variables after the two pretreatments were compared by repeated-measures ANOVA with treatment sequence as a factor. T_{max} data were compared by the Wilcoxon signed-rank test. The Pearson product-moment correlation coefficient was used to investigate the possible relationship between the pharmacokinetic variables of gemfibrozil and glimepiride. All the data were analyzed with the statistical program Systat for Windows, version 6.0.1 (SPSS Inc, Chicago, Ill). The differences were considered statistically significant when P was < .05.

RESULTS

Pharmacokinetics of glimepiride. Gemfibrozil significantly affected the pharmacokinetics of glimepiride (Table II and Fig 1). The mean AUC(0-∞) of glimepiride was increased by 23% ($P < .005$) by gemfibrozil. An increase in the AUC (range, 6%-56%) was seen in every subject (Fig 2). The mean $t_{1/2}$ of glimepiride was only slightly prolonged (from 2.1 to 2.3 hours; $P < .05$) by gemfibrozil. A statistically nonsignificant increase (14%) in the C_{max} of glimepiride was seen after gemfibrozil compared with placebo.

Pharmacodynamics of glimepiride. No statistically significant differences were found in the serum insulin or blood glucose variables between the placebo and gemfibrozil phases (Table III and Fig 3). None of the subjects experienced symptomatic hypoglycemia or any other adverse effects.

Gemfibrozil concentrations. The AUC(1-13) and C_{max} of gemfibrozil varied 2.5 and 2.8 times between the individual subjects, respectively (Table I and Fig 1). There was a tendency toward a positive correlation between the AUC(1-13) of gemfibrozil and the increase in the AUC(0-12) of glimepiride after gemfibrozil compared with placebo ($r = .58$; $P = .08$).

DISCUSSION

The results of this study demonstrate that gemfibrozil can increase the plasma concentrations of the CYP2C9 substrate glimepiride. Gemfibrozil increased the AUC of glimepiride by 23% and slightly prolonged the $t_{1/2}$. There was marked interindividual variation in the extent of the interaction, as evidenced by the range of the relative increase in the AUC of glimepiride (6%-56%). Subjects with the greatest increases in the C_{max} of glimepiride showed marked increases in the insulin response. However, the serum insulin and blood glucose responses to glimepiride were not statistically significantly affected by gemfibrozil in healthy volunteers, which may be partly explained by the relatively low degree of the pharmacokinetic interaction and variation

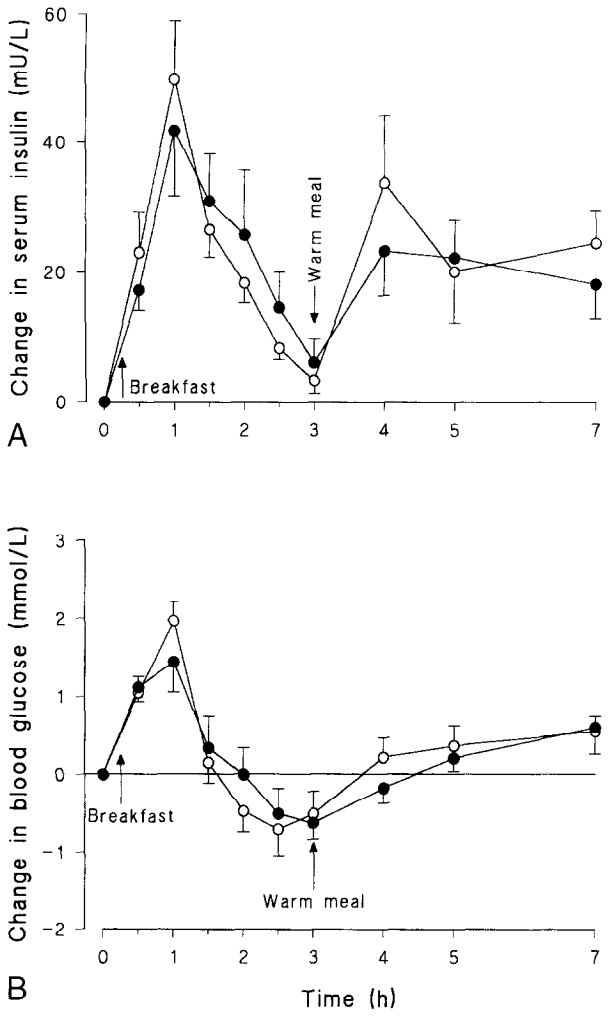

Fig 3. Mean ± SEM change in serum insulin **(A)** and blood glucose **(B)** concentrations in 10 healthy volunteers after a single oral dose of 0.5 mg glimepiride after 5 doses of placebo or 600 mg gemfibrozil administered twice daily. *Open circles*, Serum insulin or blood glucose levels during placebo; *solid circles*, serum insulin or blood glucose levels during gemfibrozil.

in the insulin and blood glucose values as a result of carbohydrate intake. It should also be noted that even when the mean AUC of glimepiride was increased by 140% by fluconazole, no statistically significant effects in the pharmacodynamics of glimepiride were seen in healthy volunteers.[4]

Glimepiride is eliminated by extensive metabolism in the liver, and CYP2C9 is involved in its biotransformation.[1] Accordingly, the potent CYP2C9 inhibitor fluconazole[2,3] considerably increases the plasma concentrations of glimepiride.[4] Recent in vitro studies indicate that gemfibrozil is also an inhibitor of CYP2C9.[11] Therefore inhibition of the CYP2C9-mediated biotransformation of glimepiride by gemfibrozil seems to be the most likely explanation for the observed interaction. Inhibition of the P-glycoprotein hardly explains the present interaction because gemfibrozil does not seem to inhibit the P-glycoprotein.[12,13]

In a previous study gemfibrozil did not significantly affect the pharmacokinetics of fluvastatin,[14] a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor that is primarily metabolized by CYP2C9.[15] On the other hand, gemfibrozil was recently shown to increase the plasma concentrations of the active HMG-CoA reductase inhibitors simvastatin acid[16] and lovastatin acid[17] but not those of the parent simvastatin and lovastatin, both of which are substrates of CYP3A4.[18,19] Gemfibrozil can cause bleeding when added to a stable regimen of warfarin, a drug metabolized mainly by CYP2C9.[7,8] Because the effect of gemfibrozil on glimepiride was modest, the interaction is probably of limited clinical significance in most cases. However, because gemfibrozil can improve insulin sensitivity in hypertriglyceridemic patients[20,21] and because of the variation in the extent of the interaction, the blood glucose–lowering effect of glimepiride may be increased during concomitant treatment with gemfibrozil in some patients. Subjects with higher gemfibrozil AUC(1-13) values tended to have a greater increase in the AUC(0-12) of glimepiride. Therefore patients with higher gemfibrozil concentrations (eg, because of impaired renal function) may be more susceptible to an interaction between gemfibrozil and glimepiride.

In conclusion, gemfibrozil modestly increases the plasma concentrations of glimepiride, possibly by inhibiting its CYP2C9-mediated biotransformation. Patients using drugs that are metabolized mainly by CYP2C9 and that have a narrow therapeutic range (eg, glimepiride, glipizide, glyburide [INN, glibenclamide], gliclazide, phenytoin, warfarin)[1,22-26] may be prone to increased effects or toxicity when gemfibrozil is added to the therapy.

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