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Lack of effect of bezafibrate and fenofibrate on the pharmacokinetics and pharmacodynamics of repaglinide

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Aims
Gemfibrozil markedly increases the plasma concentrations and blood glucose-lowering effects of repaglinide, but the effects of other fibrates on repaglinide pharmacokinetics are not known. Our aim was to investigate the effects of bezafibrate and fenofibrate on the pharmacokinetics and pharmacodynamics of repaglinide.

Methods
In a randomized, three-phase cross-over study, 12 healthy subjects received 400 mg bezafibrate, 200 mg fenofibrate or placebo once daily for 5 days. On day 5, a single 0.25 mg dose of repaglinide was ingested 1 h after the last pretreatment dose. The concentrations of plasma repaglinide, bezafibrate and fenofibrate and blood glucose were measured up to 7 h postdose.

Results
During the bezafibrate and fenofibrate phases, the total area under the concentration-time curve [AUC(0,∞)] of repaglinide was 99% (95% confidence interval of the ratio to the control phase 73, 143%) and 99% (85, 127%) of the corresponding value during the placebo (control) phase, respectively. Bezafibrate and fenofibrate had no significant effect on the peak concentration (C_{max}) of repaglinide. The mean half-life of repaglinide was 1.3 h in all phases. The blood glucose-lowering effect of repaglinide was not affected by bezafibrate or fenofibrate. The AUC(0,8 h) values for bezafibrate and fenofibrate varied 3.0-fold and 4.4-fold between individual subjects, respectively. Neither bezafibrate nor fenofibrate affected the pharmacokinetic variables of repaglinide.

Conclusions
Bezafibrate and fenofibrate do not affect the pharmacokinetics or pharmacodynamics of repaglinide.

Introduction

Repaglinide, a short-acting meglitinide analogue [1], is a novel antidiabetic agent used to normalize postprandial glucose concentrations in patients with type II diabetes [2]. It acts by enhancing glucose-stimulated insulin release from the pancreas, and its efficacy is dependent on the residual β-cell function of pancreatic islets [3, 4]. Repaglinide undergoes marked first-pass metabolism, resulting in an oral bioavailability of approximately 60% [5]. Repaglinide is completely metabolized mainly by CYP3A4 and CYP2C8 [6], and inactive metabolites are excreted primarily into faeces [7].

A recent study has revealed a clinically important interaction between gemfibrozil and repaglinide [8]. Gemfibrozil (600 mg administered twice daily) caused on average an 8-fold increase in the AUC(0,∞) of repaglinide, and greatly increased and prolonged its glucose-lowering effect. This interaction was further

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magnified when itraconazole and gemfibrozil were given together with repaglinide. The mechanism of the gemfibrozil–repaglinide interaction may involve inhibition of CYP2C8. However, as gemfibrozil is a relatively weak inhibitor of CYP2C8 *in vitro* [9], other mechanisms are possible [10–12].

Diabetic patients have an increased risk of cardiovascular morbidity and mortality [13], and benefit from active anti-atherosclerotic medical treatment [14]. Statins are most commonly used for the treatment of lipid abnormalities in diabetic patients. However, fibrates are also frequently used, because they correct low HDL cholesterol and high triglyceride concentrations, which are often associated with diabetes [15]. Thus, it is important to know whether fibrates other than gemfibrozil affect the pharmacokinetics of repaglinide. Accordingly, we have studied the effects of bezafibrate and fenofibrate on the plasma concentrations and blood glucose-lowering effect of repaglinide.

Methods

Subjects

Twelve healthy non-smoking male subjects (age range 21–26 years; weight range 58–100 kg) participated (Table 1) after giving their written informed consent. Before entering the study, the subjects were ascertained to be healthy by a medical history, a physical examination, and routine laboratory tests. None of the subjects used continuous medication, and grapefruit juice and any medication were not allowed for 2 weeks before the study. The sample size was chosen so that a possible clinically significant pharmacokinetic drug interaction could be verified statistically without the use of an unnecessarily large group of healthy subjects. The number of subjects was estimated to be sufficient to detect a 40% change in the AUC(0,∞) of repaglinide with a power of 80% (alpha-level 5%).

Study design

The study protocol was approved by the Ethics Committee for Studies in Healthy Subjects and Primary Care of the Hospital District of Helsinki and Uusimaa and the Finnish National Agency for Medicines. A randomized, placebo-controlled, cross-over study with three phases and a wash-out period of 2 weeks was carried out. The subjects received either placebo, 400 mg bezafibrate (one Bezalip 400 mg slow-release tablet, Roche, Mannheim, Germany) or 200 mg fenofibrate (one Lipanthyl 200 mg capsule, Fournier S.A., Fontaine Les Dijon, France) at 08.00 h for 5 days. On day 5, following an overnight fast, 0.25 mg repaglinide (one half of a NovoNorm 0.5 mg tablet, Novo Nordisk A/S, Bagsvaerd, Denmark) was ingested with 150 ml water at 09.00 h, 1 h after the last pretreatment dose. The timing of repaglinide administration was chosen to ensure adequate absorption of the fibrates, thus maximizing the

Table 1
Characteristics of the subjects and pharmacokinetic data for bezafibrate and fenofibrate

			Bezafibrate		Fenofibrate	
Subject	Age (years)	Weight (kg)	AUC(0,8 h) (mg l^{-1} h)	C_{max} (mg l^{-1})	AUC(0,8 h) (mg l^{-1} h)	C_{max} (mg l^{-1})
1	25	75	21.4	5.6	38.0	5.6
2	23	88	9.8	3.9	47.8	8.1
3	26	73	21.4	5.7	52.5	8.4
4	21	77	19.7	5.0	35.1	5.0
5	24	80	26.5	6.3	72.0	11.2
6	25	100	13.4	3.4	36.0	5.2
7	21	74	19.5	4.8	82.6	11.6
8	24	69	29.6	8.2	79.7	12.2
9	23	58	9.8	3.4	43.5	7.9
10	22	73	13.6	5.1	19.6	2.9
11	26	65	12.8	3.3	85.4	11.4
12	25	85	19.5	4.8	41.8	6.5
Mean ± SD	23.8 ± 1.8	76.4 ± 11.0	18.1 ± 6.3	4.9 ± 1.4	52.8 ± 21.7	8.0 ± 3.1

AUC(0,8 h), area under the concentration-time curve after the last pretreatment dose up to 8 h. C_{max} the peak concentration in plasma.

extent of any possible interaction. Food intake on day 5 was identical in all phases. Subjects were served a light standard breakfast at precisely 15 min after repaglinide administration, standard snacks rich in carbohydrates precisely 1 h and 2 h after repaglinide, a standard warm meal after 3 h and a standard light meal after 7 h. The breakfast was eaten within 10 min, the snacks within 5 min. The breakfast contained approximately 370 kcal energy, 70 g carbohydrates, 8 g protein and 6 g fat. The snacks were identical and contained about 200 kcal energy, 45 g carbohydrates, 2 g protein and 1 g fat each. During the days of repaglinide administration, the subjects were under direct medical supervision and blood glucose concentrations were monitored throughout the day. Additional carbohydrates, glucose solution for intravenous use and glucagon for intramuscular use were available, but they were not needed.

Blood sampling and determination of blood glucose concentrations

Blood samples (10 ml each) were drawn from a cannulated forearm vein prior to, and 20, 40, 60, 80, and 100 min and 2, 2.5, 3, 4, 5, and 7 h after the administration of repaglinide. Blood samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA). Glucose concentrations were measured immediately after each blood sampling using the glucose oxidase method (Precision G Blood Glucose Testing System, Medisense, Bedford, MA). Plasma was separated within 30 min after blood sampling, and was stored at −70 °C until analysis. The between-day coefficient of variation (CV) for blood glucose was 3.2% at 3.1 mmol l^{-1}, 3.6% at 5.8 mmol l^{-1} and 2.7% at 17.2 mmol l^{-1} ($n = 3$).

Determination of plasma repaglinide concentrations

Each plasma sample (0.5 ml) was placed into a 10 ml glass tube and 0.5 ml of 0.1 mol l^{-1} potassium phosphate solution (pH 4.0), and 0.6 g of solid sodium chloride salt were added. The mixture was shaken for 20 min with 6 ml diethyl ether and centrifuged for 5 min at 2000 *g*. The organic layer (5 ml) was transferred into another tube and evaporated at 30 °C to dryness under nitrogen stream. The residue was dissolved in 0.1 ml of the mobile phase and transferred into an autosampler vial.

The concentrations of repaglinide were quantified by use of PE SCIEX API 3000 liquid chromatography-tandem mass spectrometry system (Sciex Division of MDS Inc, Toronto, Ontario, Canada). Chromatography was performed on a Symmetry C_8 column (150 × 2.1 mm I.D., 3.5 μm particle size) (Waters Corp., Milford, Massachusetts, USA) using gradient elution. The mobile phase consisted of 10 mmol l^{-1} ammonium formate (pH 4.0, adjusted with 99% formic acid) and acetonitrile. The mass spectrometer was operated in the turbo ion spray mode with positive ion detection and the ion transition monitored was m/z 453 to m/z 230. This transition represents the product ion of the $[M + H]^+$ ion. The limit of quantification for repaglinide was 0.05 ng ml^{-1} and the between-day CV was 10.0% at 0.1 ng ml^{-1} and 8.5% at 2.0 ng ml^{-1} ($n = 12$).

Determination of plasma bezafibrate and fenofibrate

Plasma bezafibrate and fenofibrate concentrations on day 5 were measured by HPLC with ultraviolet detection [16]. The limit of quantification for bezafibrate was 0.1 mg l^{-1}, and the between-day CV was 8.9% at 0.2 mg l^{-1}, 1.9% at 4.4 mg l^{-1} and 4.7% at 10.2 mg l^{-1} ($n = 5$). For fenofibrate, the limit of quantification was 0.1 mg l^{-1}, and the between-day CV was 11.0% at 0.3 mg l^{-1}, 2.5% at 3.5 mg l^{-1} and 2.3% at 8.8 mg l^{-1} ($n = 7$).

Pharmacokinetics

The pharmacokinetics of repaglinide were characterized by the peak concentration in plasma (C_{max}), the time to C_{max} (t_{max}), the area under the concentration-time curve from 0 to 7 h [AUC(0,7 h)] and from 0 h to infinity [AUC(0,∞)], and the elimination half-life ($t_{1/2,z}$). Values for C_{max} and t_{max} were taken directly from the raw data. For each subject, the terminal log-linear part of the concentration-time curve was identified visually, and the elimination rate constant (λ_z) was determined from these data using linear regression analysis. The $t_{1/2,z}$ was calculated from the equation $t_{1/2,z} = \ln 2/\lambda_z$. AUC values were determined using the linear trapezoidal rule for the rising phase of the plasma repaglinide 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 λ_z. The pharmacokinetics of bezafibrate and fenofibrate were characterized by C_{max} and AUC(0,8 h). All pharmacokinetic calculations were performed using the program MK-Model, version 5.0 (Biosoft, Cambridge, UK).

Pharmacodynamics

The pharmacodynamics of repaglinide were characterized by baseline, mean and minimum blood glucose concentrations. The baseline and minimum values were taken directly from the original data, and the mean concentration was calculated by dividing the area under the blood glucose concentration-time curve from 0 to 7 h by the corresponding time interval.

Statistical analysis

Results are expressed as mean values ± SD. The pharmacokinetic and pharmacodynamic variables between the placebo and bezafibrate or fenofibrate phases (the AUC and C_{max} of repaglinide after log-transformation) were compared using repeated-measures analysis of variance (ANOVA) and a paired *t*-test with the Bonferroni correction. For all variables, except t_{max}, 95% confidence intervals (CI) were calculated on the mean differences between the placebo and bezafibrate or fenofibrate phases. The t_{max} values were compared with Friedman's two-way ANOVA followed by the Wilcoxon signed-rank test with the Bonferroni correction. The analyses were performed using the statistical program Systat for Windows, V6.0.1 (SPSS Inc., Chicago, Ill). Differences were considered statistically significant when P was < 0.05.

Results

Bezafibrate and fenofibrate had no statistically significant effects on any of the pharmacokinetic variables for repaglinide (Figure 1, Table 2). In the bezafibrate and fenofibrate phases, the AUC(0,∞) for repaglinide was 99.1% (95% confidence interval of the ratio to the control phase 73, 143%) and 99.4% (85, 127%) of the corresponding value during the placebo (control) phase, respectively. The $t_{1/2,z}$ of repaglinide was 1.3 ± 0.4 h, 1.3 ± 0.3 h and 1.3 ± 0.3 h in the placebo, bezafibrate and fenofibrate phases, respectively. The mean C_{max} values of repaglinide were slightly but nonsignificantly higher during the bezafibrate (3.0 ± 1.4 ng ml^{-1}) and fenofibrate (3.3 ± 1.6 ng ml^{-1}) phases than during the placebo phase (2.8 ± 1.4 ng ml^{-1}). The AUC(0,7 h) values of repaglinide differed from the AUC(0,∞) values by less than 0.1% and are not presented.

Bezafibrate and fenofibrate did not change the effect of repaglinide on the blood glucose concentrations, when compared with placebo. Neither baseline, mean nor minimum blood glucose concentrations were changed significantly by bezafibrate or fenofibrate (Figure 2, Table 2). None of the subjects had symptomatic hypoglycaemia.

The mean plasma concentrations of bezafibrate and fenofibrate are presented in Figure 2. The AUC(0,8 h) values of bezafibrate and fenofibrate varied 3.0-fold and 4.4-fold and C_{max} values varied 2.5-fold and 4.2-fold between subjects, respectively (Table 1).

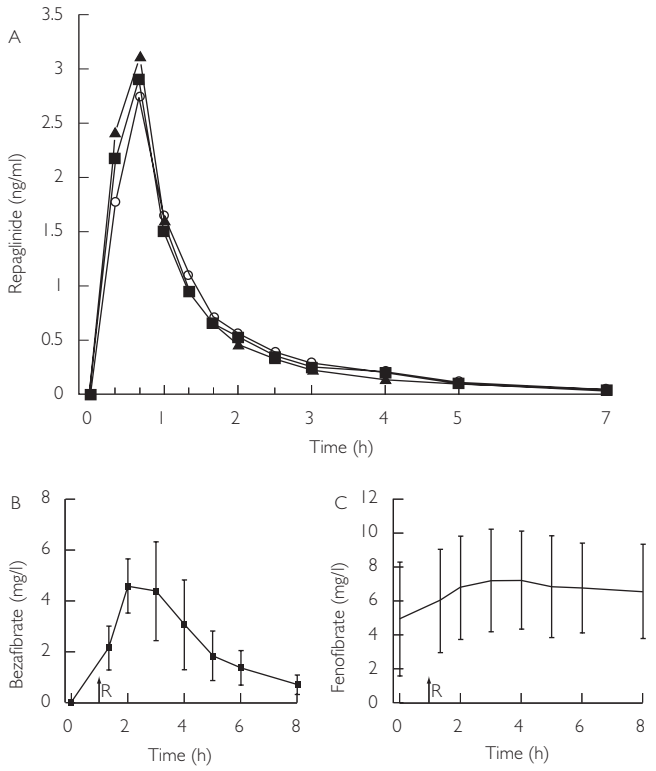

Figure 1

(A) Mean plasma concentrations of repaglinide in 12 healthy volunteers after a single 0.25 mg oral dose of repaglinide, alone or with 400 mg bezafibrate or 200 mg fenofibrate once daily for 5 days. ○, repaglinide alone; ■, repaglinide with bezafibrate; ▲, repaglinide with fenofibrate. For clarity, only mean values are presented. Mean (± SD) plasma concentrations of (B) bezafibrate and (C) fenofibrate after the last dose, in their respective phases. Time zero in Figures B and C refers to administration of the fibrates, i.e. 1 h before the administration of repaglinide (R)

Discussion

Tight glycaemic control in type II diabetes is important in the prevention of microvascular disease [17, 18]. Management of dyslipidaemia, and the prevention of macrovascular disease is less often emphasized, although equally as important for hyperlipidaemic diabetic patients [14, 19, 20]. The prevalence of hypertriglyceridaemia and low HDL cholesterol concentrations is twice as high in diabetic as in nondiabetic groups [21]. Therefore, it is likely that many diabetic patients benefit from treatment with fibrates, and it is important to characterize the interaction potential of different fibrates with drugs that are commonly used in this patient group.

In this study, we found that administration of the usual therapeutic doses of bezafibrate and fenofibrate had no significant effect on the pharmacokinetics and pharmacodynamics of repaglinide in healthy subjects. These fibrates did not influence the AUC, C_{max} or $t_{1/2,z}$ of repaglinde. Furthermore, blood glucose concentration remained unchanged. This lack of interaction is clearly at variance with the potent effect of gemfibrozil on the

Table 2
Pharmacokinetic and pharmacodynamic data for repaglinide after a single 0.25 mg oral dose of the drug in 12 healthy volunteers, alone (placebo) or with 400 mg bezafibrate or 200 mg fenofibrate once daily for 5 days

Variable	Placebo phase	Bezafibrate phase	Fenofibrate phase
Repaglinide pharmacokinetics			
C_{max} (ng ml^{-1})	2.8 ± 1.4	3.0 ± 1.4	3.3 ± 1.6
95% CI*		78, 154%	96, 154%
t_{max} (min)	40 (20–40)	40 (20–40)	40 (20–40)
$t_{1/2,z}$ (h)	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.3
95% CI*		77, 123%	69, 115%
AUC(0, ∞) (ng ml^{-1} h)	3.7 ± 2.0	3.6 ± 1.8	3.7 ± 1.8
95% CI*		73, 143%	85, 127%
Blood glucose			
Baseline concentration (mmol l^{-1})	4.8 ± 0.4	4.7 ± 0.6	4.9 ± 0.4
95% CI*		83, 106%	94, 108%
Mean concentration (0–7 h) (mmol l^{-1})	4.6 ± 0.5	4.6 ± 0.5	4.7 ± 0.4
95% CI*		96, 107%	96, 109%
Minimum concentration (mmol l^{-1})	3.5 ± 0.5	3.8 ± 0.5	3.6 ± 0.3
95% CI*		97, 117%	94, 109%

*Values shown are means ± SD; t_{max} data are given as median (range). Baseline concentration: fasting concentration on day 5 before repaglinide administration. * 95% confidence interval of the ratio to the control phase (% of control).*

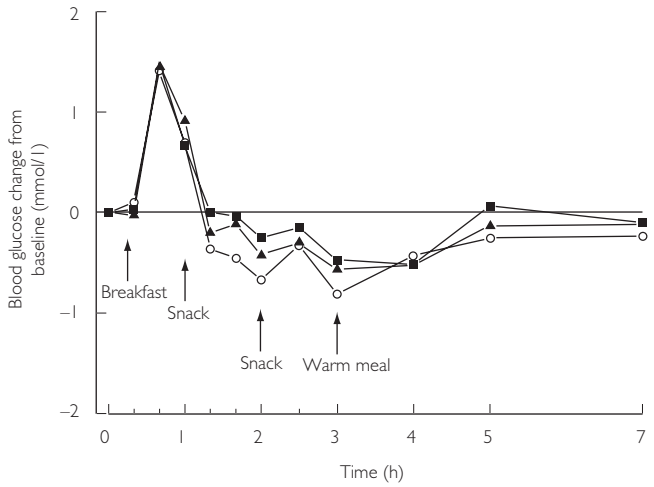

Figure 2
Mean change in blood glucose concentrations in 12 healthy volunteers after a single 0.25 mg oral dose of repaglinide, alone or with 400 mg bezafibrate or 200 mg fenofibrate once daily for 5 days. ○, alone; ■, after bezafibrate; ▲, after fenofibrate. For clarity, only mean values are presented

pharmacokinetics of repaglinide [8]. For safety reasons, only a small, 0.25 mg dose of repaglinide was used in the present study in healthy subjects, who are more sensitive than diabetic patients to the pharmacodynamic effects of the drug. However, as the pharmacokinetics of repaglinide are linear, it is reasonable to assume that the present findings can be extrapolated to normal therapeutic doses (0.5–4 mg) of the drug. Previous studies have shown that repaglinide (0.5–4 mg) improves insulin secretion and reduces prandial hyperglycaemia dose-dependently [22].

The AUC and C_{max} values for bezafibrate and fenofibrate, as well as their interindividual variation, were comparable with those found in previous studies [23, 24]. Based on individual plasma concentrations, compliance to bezafibrate and fenofibrate therapy was good, indicating that the lack of an interaction was not caused by a failure to take bezafibrate or fenofibrate.

CYP3A4 and CYP2C8 mainly metabolize repaglinide *in vitro* [6]. However, *in vivo*, inhibitors of CYP3A4 have caused only moderate increases in the plasma concentrations of repaglinide. Thus, clarithromycin [25] and itraconazole [8] increased the AUC(0,∞) of repaglinide by about 40%. On the other hand, gemfibrozil causes an 8-fold increase in the AUC(0,∞) of repaglinide and greatly enhances and prolongs its glucose-lowering effect [8]. In diabetic patients using both gemfibrozil and repaglinide, several cases of serious hypoglycaemia have been reported [26]. The combination of itraconazole and gemfibrozil causes an even larger increase in the AUC(0,∞) of about 20-fold and

greatly enhances the effects of repaglinide [8]. Gemfibrozil inhibits CYP2C8 *in vitro* [9] and *in vivo* [27], but does not affect CYP3A4, at least not *in vitro* [28]. Gemfibrozil is also known to inhibit other CYP enzymes [10], UDP-glucuronosyltransferases [11], and certain transport proteins *in vitro* [12]. Thus, there are several possible mechanisms for the gemfibrozil–repaglinide interaction. Trimethoprim, a selective but not very potent CYP2C8 inhibitor [29], increases the AUC(0,∞) of repaglinide on average by 61% [30]. Furthermore, a polymorphism in the *CYP2C8* gene is associated with decreased plasma concentrations of repaglinide [31]. Thus, CYP2C8 seems to have a central role in the metabolism of repaglinide in humans *in vivo*, whereas the contribution of CYP3A4 is probably of limited significance.

Gemfibrozil greatly increases the plasma concentrations of several statins [24, 25, 32, 33], whereas bezafibrate and fenofibrate appear devoid of this effect [33]. Both repaglinide and some of the statins (e.g. cerivastatin) or their active acid metabolites (e.g. simvastatin acid) are substrates of CYP2C8 [9, 34, 35]. Furthermore, the plasma concentrations of the CYP2C8 substrate rosiglitazone are increased by gemfibrozil [36].

The present finding that neither bezafibrate nor fenofibrate interact adversely with repaglinide has important therapeutic consequences. Many diabetic patients using oral hypoglyacemic agents have hypertriglyceridaemia and low HDL cholesterol concentrations, and may be prescribed fibrates. However, because of the potentially hazardous interaction between gemfibrozil and repaglinide, the concomitant use of these drugs is discouraged or even contraindicated in some countries (EU). In contrast, bezafibrate and fenofibrate can be used together with repaglinide due to the lack of interaction.

In conclusion, the administration of bezafibrate or fenofibrate does not increase the plasma concentrations of repaglinide or change its blood glucose-lowering effects in healthy subjects.

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