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Short Communication

Gemfibrozil considerably increases the plasma concentrations of rosiglitazone

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Abstract

Aims/hypothesis. Our aim was to investigate possible interaction between gemfibrozil and rosiglitazone, a thiazolidinedione antidiabetic drug.
Methods. In a randomised crossover study with two phases, 10 healthy volunteers took 600 mg gemfibrozil or placebo orally twice daily for 4 days. On day 3, they ingested a single 4 mg dose of rosiglitazone. Plasma rosiglitazone and its *N*-desmethyl metabolite concentrations were measured for up to 48 h.
Results. Gemfibrozil raised the mean area under the plasma rosiglitazone concentration-time curve (AUC) 2.3-fold (range 1.5- to 2.8-fold; p=0.00002) and prolonged the elimination half-life ($t_{1/2}$) of rosiglitazone from 3.6 to 7.6 h (p=0.000002). The peak plasma rosiglitazone concentration (C_{max}) was increased only 1.2-fold (range 0.9- to 1.6-fold; p=0.01) by gemfibrozil, but gemfibrozil raised the plasma rosiglitazone concentration measured 24 h after dosing (C_{24}) 9.8-fold (range, 4.5- to 33.6-fold; p=0.00008). In addition, gemfibrozil prolonged the t_{max} of *N*-desmethylrosiglitazone from 7 to 12 h and reduced the *N*-desmethylrosiglitazone/rosiglitazone $AUC_{0–48}$ ratio by 38% (p<0.01).
Conclusions/interpretation. Gemfibrozil raises the plasma concentrations of rosiglitazone probably by inhibiting the CYP2C8-mediated biotransformation of rosiglitazone. Co-administration of gemfibrozil, or another potent inhibitor of CYP2C8, and rosiglitazone could increase the efficacy but also the risk of concentration-dependent adverse effects of rosiglitazone. [Diabetologia (2003) 46:1319–1323]

Keywords CYP2C8, CYP2C9, drug interaction, gemfibrozil, pharmacokinetics, rosiglitazone.

Rosiglitazone is an insulin-sensitising antidiabetic drug of the thiazolidinedione class. It is almost completely bioavailable from the gastrointestinal tract and is completely metabolised in humans [1]. In vitro studies suggest that cytochrome P450 (CYP) 2C8 is primarily responsible for the metabolism of rosiglitazone, with CYP2C9 contributing to its metabolism to a lesser extent [2]. The lipid-lowering drug gemfibrozil inhibits both CYP2C8 [3] and CYP2C9 [4] and was recently found to dangerously increase the plasma concentrations of the meglitinide analogue antidiabetic drug repaglinide (a substrate of CYP2C8) [5]. As fibrates are widely used to lower high serum triglyceride concentrations in patients with Type 2 diabetes mellitus, we found it important to investigate the possible interaction between gemfibrozil and rosiglitazone.

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Abbreviations: AUC, area under the concentration-time curve from time zero to infinity; $AUC_{0–13}$, area under the concentration-time curve from time zero to 13 h; $AUC_{0–48}$, area under the concentration-time curve from time zero to 48 h; C_{24}, concentration 24 h after dosing; C_{max}, peak concentration; CYP, cytochrome P450; t_{max}, time to peak concentration; $t_{1/2}$, elimination half-life.

Subjects and methods

Subjects. After giving written informed consent, 10 healthy volunteers participated in the study (9 men, 1 woman; age range 21–26 years; weight 46–77 kg). They were ascertained to be healthy by medical history, physical examination, and routine laboratory tests. Of the subjects two were smokers, but none used any continuous medication. The study protocol was approved by the Ethics Committee for Studies in Healthy Subjects and Primary Care of the Helsinki and Uusimaa Hospital District.

Study design. A randomised, placebo-controlled crossover study with two phases and a washout period of 2 weeks was carried out. The volunteers took twice daily at 8:00 a.m. and 8:00 p.m. for 4 days either 600 mg gemfibrozil (Lopid, Parke-Davis, Freiburg, Germany) or placebo. On day 3, at 9:00 a.m., after an overnight fast and 1 h after a pretreatment dose (gemfibrozil or placebo), each ingested a single 4 mg dose of rosiglitazone (Avandia 4 mg tablet, SmithKlineBeecham, Brentford, UK). Food intake on day 3 was standardised and identical during both phases and comprised of a warm meal 3 h after rosiglitazone intake and a light meal after 7 h.

Blood sampling and determination of drug concentrations. Timed venous blood samples were collected before the administration of rosiglitazone and for up to 48 h thereafter. Plasma was separated and the samples stored deep frozen until analysis. Plasma rosiglitazone and its *N*-desmethyl metabolite concentrations were measured by HPLC with fluorescence and ultraviolet detection [1, 6]. Pioglitazone served as internal standard. The limit of quantification for rosiglitazone was 1.0 ng/ml and the between-day CV was below 12% (n=6). *N*-desmethylrosiglitazone is given in arbitrary units (U) relative to the ratio of the peak height of *N*-desmethylrosiglitazone to that of the internal standard in the chromatogram. Plasma gemfibrozil concentrations were determined by HPLC with ultraviolet detection and ibuprofen as internal standard. The limit of quantification for gemfibrozil was 0.1 μg/ml and the CV below 5% (n=7).

Pharmacokinetics. The pharmacokinetics of rosiglitazone were characterised by peak concentration in plasma (C_{max}), concentration 24 h after dosing (C_{24}), time to C_{max} (t_{max}), AUC from time zero to 48 h ($AUC_{0–48}$) or infinity (AUC) and by elimination half-life ($t_{1/2}$); those of *N*-desmethylrosiglitazone by C_{max}, t_{max}, $AUC_{0–48}$, $t_{1/2}$ and *N*-desmethylrosiglitazone/rosiglitazone $AUC_{0–48}$ ratio. The pharmacokinetics of gemfibrozil on day 3 were characterised by C_{max} and $AUC_{0–13}$. The C_{max} and t_{max} values were taken directly from original data. The terminal log-linear part of the concentration-time curve was 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 $t_{1/2}$ was calculated by the equation $t_{1/2}=\ln 2/k_e$. 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.

Statistical analysis. Results are expressed as mean values ± SD in the text and table and, for clarity, as mean values ± SEM in the figure (n equals 10 unless otherwise indicated). For all variables except t_{max}, 95% CI were calculated on the mean differences between placebo and gemfibrozil phases. Statistical comparisons between the phases were made with paired t-test or, in the case of t_{max}, with the Wilcoxon signed-rank test. The Pearson correlation coefficient was used to investigate possible relationships between the pharmacokinetic variables of gemfibrozil and rosiglitazone. The differences were considered statistically significant at a p value of less than 0.05.

Results

Pharmacokinetics of rosiglitazone. The plasma concentrations of rosiglitazone were increased by gemfi-

Table 1. Pharmacokinetic variables of rosiglitazone in 10 healthy volunteers after a single 4 mg oral dose of rosiglitazone on day 3 of a 4-day treatment with gemfibrozil (600 mg bid) or placebo

Variable	Placebo phase (control)	Gemfibrozil phase	Gemfibrozil phase percentage of control (range)	Mean difference between phases (95% CI)	p
Rosiglitazone					
C_{max} (ng/ml)	285±50	349±94	122% (93–161%)	64 (18,110)	0.01
C_{24} (ng/ml)	3.7±2.2	36±16	982% (446–3356%)	32 (22,43)	0.00008
t_{max} (h)	1 (0.5–2)	1 (0.5–1.5)	–	–	0.23
$t_{1/2}$ (h)	3.6±0.5	7.6±1.5	212% (162–249%)	4.0 (3.2,4.9)	0.000002
$AUC_{0–48}$ (ng·h/ml)	1554±366	3499±1001	225% (150–277%)	1946 (1408,2484)	0.00002
AUC (ng·h/ml)	1556±368	3563±1054	229% (151–279%)	2007 (1434,2580)	0.00002
N-desmethylrosiglitazone					
C_{max} (U/ml)	5.8±0.6	5.8±0.7	99% (87–112%)	–0.1 (–0.5,0.3)	0.76
$t_{1/2}$ (h)	16.3±2.6	NE[a]	–	–	–
t_{max} (h)	7 (5–12)	12 (12–24)	–	–	0.007
$AUC_{0–48}$ (U·h/ml)	157±19	213±26	136% (120–152%)	56 (43,69)	0.000004
$AUC_{0–48}$ ratio (U/ng) (metabolite/rosiglitazone)	0.103±0.012	0.064±0.014	62% (49–95%)	–0.039 (–0.049,–0.029)	0.000009

Values shown as means ± SD; t_{max} data as median (range)
[a] NE, the $t_{1/2}$ of *N*-desmethylrosiglitazone could not be estimated during the gemfibrozil phase

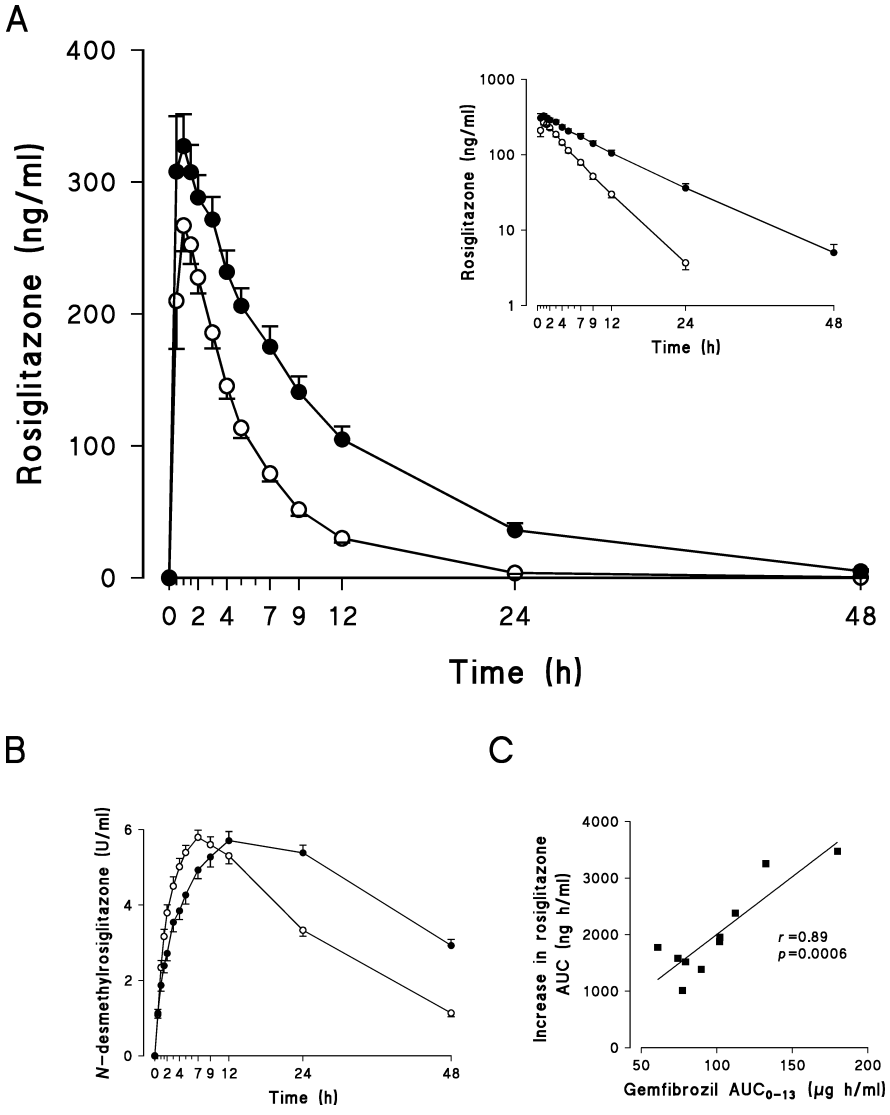

Fig. 1A–C. Mean (± SEM) plasma concentrations of rosiglitazone (*inset* depicts the same data on a semi-logarithmic scale) (**A**) and *N*-desmethylrosiglitazone (**B**), and relationship between the $AUC_{0–13}$ of gemfibrozil and the increase in the AUC of rosiglitazone caused by gemfibrozil (**C**) in 10 healthy volunteers after a single oral dose of 4 mg rosiglitazone during placebo (*open circles*) and gemfibrozil 600 mg twice a day (*solid circles*) treatments

brozil compared with placebo (Fig. 1A, Table 1). Gemfibrozil raised the mean AUC and C_{max} of rosiglitazone 2.3-fold (range 1.5- to 2.8-fold; p=0.00002) and 1.2-fold (range 0.9- to 1.6-fold; p=0.01), respectively. The plasma concentration of rosiglitazone, measured 24 h after dosing (C_{24}), was 9.8-fold (range, 4.5- to 33.6-fold) higher during the gemfibrozil phase than during the placebo phase (p=0.00008). The $t_{1/2}$ of rosiglitazone was prolonged from 3.6 to 7.6 h by gemfibrozil (p=0.000002). In addition, gemfibrozil prolonged the t_{max} of *N*-desmethylrosiglitazone from 7 to 12 h (p=0.007) and reduced the *N*-desmethylrosiglitazone/rosiglitazone $AUC_{0–48}$ ratio by 38% (p=0.000009) (Fig. 1B, Table 1).

Pharmacokinetics of gemfibrozil. The $AUC_{0–13}$ and C_{max} of gemfibrozil on day 3 were 101±35 µg·h/ml (range, 64 to 187) and 27.7±8.6 µg/ml (range, 18.6 to 45.4), respectively. The $AUC_{0–13}$ of gemfibrozil on day 3 correlated with the change in the C_{max} (r=0.78, p=0.008) and AUC (r=0.89, p=0.0006) of rosiglitazone (Fig. 1C).

Discussion

This study shows that administration of usual therapeutic doses of gemfibrozil considerably increases the plasma concentrations of rosiglitazone. The AUC of rosiglitazone was considerably increased and the $t_{1/2}$ prolonged by gemfibrozil. Gemfibrozil had only a minor effect on the C_{max} of rosiglitazone, but greatly increased the C_{24} of rosiglitazone (about 10-fold). Furthermore, gemfibrozil reduced the *N*-desmethylrosig-

litazone/rosiglitazone $AUC_{0–48}$ ratio and prolonged the t_{max} of *N*-desmethylrosiglitazone, indicating that it inhibits the metabolism of rosiglitazone. There was considerable interindividual variability in the extent of the interaction between gemfibrozil and rosiglitazone: the relative increase in the AUC of rosiglitazone ranged from 51 to 179%.

The oral bioavailability of rosiglitazone is nearly 100% and it is not significantly metabolised during the first-pass [1]. Thus it is not surprising that gemfibrozil only mildly affected the C_{max} of rosiglitazone. In contrast, gemfibrozil greatly reduced the systemic elimination of rosiglitazone. From the systemic circulation, rosiglitazone is eliminated completely by metabolism [1]. In vitro studies have shown that CYP2C8 is the principal enzyme responsible for the elimination of rosiglitazone with CYP2C9 contributing to it to a lesser extent [2]. Gemfibrozil inhibits both CYP2C8 and CYP2C9 in vitro [3, 4]. In vivo, gemfibrozil has had its greatest effects on the pharmacokinetics of drugs that are metabolised mainly by CYP2C8, such as cerivastatin and repaglinide. An identical gemfibrozil treatment as that used in this study increased the mean AUC of cerivastatin about five-fold [7] and that of repaglinide by about eight-fold [5]. Gemfibrozil only moderately increased the AUC of glimepiride (by 23%), a sulfonylurea antidiabetic drug metabolised mainly by CYP2C9 [8].

In clinical practice, rosiglitazone is administered on a regular basis and its effects on for example, blood glucose concentrations are achieved gradually, reaching a plateau after 8 to 12 weeks. The relative increase in the steady-state plasma concentration of rosiglitazone caused by gemfibrozil during long-term administration should be equal to that in the total AUC of rosiglitazone after a single dose. It is, however, possible that a higher dose or longer use of gemfibrozil would produce an even greater interaction with rosiglitazone than that seen in our study. Therefore, it is reasonable to assume that concomitant use of gemfibrozil and rosiglitazone can increase the efficacy and the risk of concentration-dependent adverse effects of rosiglitazone.

The most common serious adverse effect of the newer thiazolidinediones rosiglitazone and pioglitazone has been pulmonary and peripheral oedema [9]. These adverse effects seem to be dose- (concentration) dependent and develop within the first few months of drug initiation or dose increment. The exact mechanism of thiazolidinedione-associated oedema is not known, but a recent in vitro study showed that rosiglitazone increases pulmonary endothelial permeability in a concentration-dependent manner [10]. In our study in young healthy subjects, the highest individual plasma concentration of rosiglitazone was nearly 2 μmol/l after a single dose of 4 mg rosiglitazone during the gemfibrozil phase. Thus, it is reasonable to assume that in some patients on gemfibrozil and a daily rosiglitazone dose of 8 mg, concentrations of up to 4 to 10 μmol/l of rosiglitazone can occur. In one in vitro study, incubation of pulmonary artery endothelial cells for 4 h with 10μmol/l of rosiglitazone increased transendothelial albumin loss by 115% while 1 μmol/l caused a nonsignificant (13%) mean increase in permeability [10]. Thus, during concomitant use of clinically relevant doses of rosiglitazone and gemfibrozil, the plasma concentrations of rosiglitazone can increase to the level shown in vitro to increase endothelial permeability.

Due to the possibility of an increased risk of adverse effects, it could be advisable to avoid coadministration of gemfibrozil and rosiglitazone. Alternatively, if gemfibrozil treatment is started on a patient using rosiglitazone, rosiglitazone dose should be reduced by about 50 to 70% and the patient carefully monitored for signs and symptoms of adverse effects of rosiglitazone. The $AUC_{0–13}$ of gemfibrozil correlated with the change in the AUC and C_{max} of rosiglitazone. Thus, patients with higher gemfibrozil concentrations (e.g., due to impaired renal function) could be more susceptible to an interaction between gemfibrozil and rosiglitazone. It should be noted that the potential of other fibrates to interact with rosiglitazone might be different from that of gemfibrozil, but currently no data about their possible interactions with rosiglitazone have been published.

In conclusion, gemfibrozil raises the plasma concentrations of rosiglitazone probably by inhibiting its CYP2C8-mediated biotransformation. Coadministration of gemfibrozil, or another potent inhibitor of CYP2C8, and rosiglitazone could be associated with increased efficacy but also an increased risk of concentration-dependent adverse effects of rosiglitazone.

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