Rapid Communication

Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide

M. Niemi, J. T. Backman, M. Neuvonen, P. J. Neuvonen

Department of Clinical Pharmacology, Helsinki University Central Hospital, 00029, HUS, Finland

Abstract

Aims/hypothesis. Our aim was to investigate possible interactions of gemfibrozil, itraconazole, and their combination with repaglinide.

Methods. In a randomised crossover study, 12 healthy volunteers received twice daily for 3 days either 600 mg gemfibrozil, 100 mg itraconazole (first dose 200 mg), both gemfibrozil and itraconazole, or placebo. On day 3 they ingested a 0.25 mg dose of repaglinide. Plasma drug and blood glucose concentrations were followed for 7 h and serum insulin and C-peptide concentrations for 3 h postdose.

Results. Gemfibrozil raised the area under the plasma concentration-time curve (AUC) of repaglinide 8.1-fold (range 5.5- to 15.0-fold; $p<0.001$) and prolonged its half-life ($t_{1/2}$) from 1.3 to 3.7 h ($p<0.001$). Although itraconazole alone raised repaglinide AUC only 1.4-fold (1.1- to 1.9-fold; $p<0.001$), the gemfibrozil-itraconazole combination raised it 19.4-fold

(12.9- to 24.7-fold) and prolonged the $t_{1/2}$ of repaglinide to 6.1 h ($p<0.001$). Plasma repaglinide concentration at 7 h was increased 28.6-fold by gemfibrozil and 70.4-fold by the gemfibrozil-itraconazole combination ($p<0.001$). Gemfibrozil alone and in combination with itraconazole considerably enhanced and prolonged the blood glucose-lowering effect of repaglinide; i.e., repaglinide became a long-acting and stronger antidiabetic.

Conclusion/interpretation. Clinicians should be aware of this previously unrecognised and potentially hazardous interaction between gemfibrozil and repaglinide. Concomitant use of gemfibrozil and repaglinide is best avoided. If the combination is considered necessary, repaglinide dosage should be greatly reduced and blood glucose concentrations carefully monitored. [Diabetologia (2003) 46:347–351]

Keywords CYP2C8, CYP3A4, drug interaction, gemfibrozil, hypoglycaemia, itraconazole, repaglinide.

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Corresponding author: P. J. Neuvonen, Department of Clinical Pharmacology, Helsinki University Central Hospital, P.O. Box 340, 00029, HUS, Finland
E-mail: pertti.neuvonen@hus.fi

Abbreviations: AUC, area under the concentration-time curve from time zero to infinity; AUC_{0-7} , area under the concentration-time curve from time zero to 7 h; AUC_{0-8} , area under the concentration-time curve from time zero to 8 h; C_7 , concentration at 7 h; C_{max} , peak concentration; CYP, cytochrome P450; t_{max} , time to peak concentration; $t_{1/2}$, elimination half-life.

Repaglinide is a short-acting meglitinide analogue antidiabetic drug, recommended to be taken preprandially to lower postprandial hyperglycaemia [1]. Repaglinide is completely metabolised, and cytochromes P-450 (CYP) 2C8 and 3A4 participate in its biotransformation in vitro [2]. Fibrates like gemfibrozil are widely used in the treatment of diabetic dyslipidaemia, and gemfibrozil was recently found to inhibit CYP2C8 [3, 4]. Several commonly used drugs, such as the antimycotic itraconazole, are inhibitors of CYP3A4 [5]. Because many patients with Type 2 diabetes using repaglinide are likely to take concomitantly drugs that inhibit CYP2C8 or CYP3A4 enzymes, we studied the possible interactions of gemfibrozil, itraconazole, and their combination with repaglinide.

Fig. 1A–D. Means ($\pm$ SEM) plasma concentrations of repaglinide (**A**), its aromatic amine metabolite (M1) (**B**), change in blood glucose concentrations (**C**) and relationship between repaglinide C_{max} and minimum blood glucose concentration (**D**) in 12 healthy volunteers after a single oral dose of 0.25 mg repaglinide during placebo (open circles), itraconazole 100 mg bid (solid squares), gemfibrozil 600 mg bid (solid triangles), and combined itraconazole and gemfibrozil (solid stars) treatments

Subjects and methods

Subjects. Twelve healthy volunteers (4 men, 8 women; age 20–24 years; weight 46–84 kg) participated in the study after giving written informed consent. They were ascertained to be healthy by medical history, physical examination, and laboratory tests. None was on any continuous medication. Two subjects were tobacco smokers. The local ethics committee approved the study.

Design. A randomised, placebo-controlled crossover study with four phases and a washout period of 4 weeks was carried out. The volunteers took twice daily for 3 days either 600 mg gemfibrozil (Lopid, Parke-Davis, Freiburg, Germany), 100 mg itraconazole (first dose 200 mg; Sporanox, Janssen-Cilag, Borgo San Michele, Italy), both gemfibrozil and itraconazole, or placebo. On day 3, at 9 a.m., after an overnight fast and 1 h

after the last pretreatment dose, each ingested a single 0.25 mg dose of repaglinide (one half of a Novonorm 0.5 mg tablet, NovoNordisk, Bagsvaerd, Denmark). Food intake on day 3 was identical during all phases and comprised a breakfast 15 min after repaglinide, snacks 1 and 2 h later, and a meal after 3 h. Additional carbohydrates were given for symptomatic hypoglycaemia when necessary.

Blood sampling and analyses. Timed venous blood samples were collected before repaglinide administration and for 7 h thereafter. Blood glucose concentrations were measured immediately after sampling by the glucose oxidase method. The between-day CV for blood glucose was below 8%. Plasma and serum samples were stored deep frozen until analysis. Insulin and C-peptide concentrations were measured up to 3 h by fluoroimmunoassay methods (AutoDELFA, Wallac Oy, Turku, Finland), with CVs below 4%. Plasma repaglinide and its amine metabolite (M1) concentrations were measured using the liquid chromatography-ion-spray tandem mass spectrometer PE SCIEX API 3000 (MDS Sciex, Concord, ON, Canada) [6]. Nateglinide served as the internal standard. The ion transitions monitored were m/z 453 to 230 for repaglinide, m/z 385 to 162 for M1, and m/z 318 to 69 for nateglinide. The limit of quantification was 0.1 ng/ml for repaglinide (CV below 13%). M1 is given in arbitrary units (U) relative to the peak height in the chromatogram. Plasma gemfibrozil, itraconazole, and hydroxyitraconazole concentrations were determined by HPLC [4, 5]. The limit of quantification was 0.1 μ g/ml for gemfibrozil (CV below 11%) and 10 ng/ml for itraconazole and hydroxyitraconazole (CV below 6%).

Table 1. Pharmacokinetic and pharmacodynamic variables of repaglinide, itraconazole, hydroxyitraconazole, and gemfibrozil

Variable	Placebo phase (control)	Itraconazole phase	Gemfibrozil phase	Itraconazole + gemfibrozil phase
Repaglinide				
$C_{\max}$ (ng/ml)	6.1±2.7	9.0±3.5 ^a	14.6±4.5 ^{c, f}	16.8±5.4 ^{c, f}
C_7 (ng/ml)	0.11±0.03	0.13±0.03	3.0±0.5 ^{c, f}	7.4±1.0 ^{c, f, i}
$t_{\max}$ (min)	40 (20–40)	40 (20–40)	40 (40–60)	40 (40–60)
$t_{1/2}$ (h)	1.3±0.4	1.6±0.5	3.7±1.5 ^{c, e}	6.1±2.6 ^{c, f, h}
AUC _{0–7} (ng·h/ml)	7.6±3.8	10.8±5.6 ^c	44.8±13.8 ^{c, f}	75.6±27.0 ^{c, f, i}
AUC (ng·h/ml)	7.9±4.0	11.1±5.8 ^c	63.9±31.6 ^{c, f}	152.5±97.9 ^{c, f, i}
M1				
$C_{\max}$ (U/ml)	0.35±0.11	0.11±0.03 ^c	0.91±0.26 ^{c, f}	0.16±0.05 ^{c, d, i}
$t_{\max}$ (min)	40 (40–120)	60 (40–120)	60 (40–120)	165 (100–420) ^{a, d, g}
AUC _{0–7} (U·h/ml)	0.59±0.21	0.18±0.09 ^c	3.39±1.14 ^{c, f}	0.80±0.23 ^{f, i}
M1 to repaglinide AUC _{0–7} ratio (U/ng)	0.083±0.024	0.017±0.005 ^c	0.077±0.021 ^f	0.011±0.004 ^{c, d, i}
Blood glucose				
Baseline concentration (mmol/l)	5.2±0.5	5.2±0.3	5.0±0.4	5.1±0.4
Mean concentration (0–7 h) (mmol/l)	4.7±0.5	4.9±0.5	3.9±0.5 ^{c, f}	3.5±0.4 ^{c, f}
Minimum concentration (mmol/l)	3.8±0.5	3.7±0.7	2.9±0.4 ^{c, e}	2.3±0.4 ^{c, f, h}
C_7 (mmol/l)	4.8±0.4	5.1±0.9	4.1±0.6 ^{b, e}	3.2±0.8 ^{c, f, h}
Insulin				
Baseline concentration (pmol/l)	31±15	21±14	32±24	22±13
Mean concentration (0–3 h) (pmol/l)	178±58	210±97	268±96 ^b	275±119 ^{a, e}
C-peptide				
Baseline concentration (nmol/l)	0.49±0.11	0.45±0.10	0.50±0.17	0.45±0.07
Mean concentration (0–3 h) (nmol/l)	1.57±0.28	1.73±0.44	2.04±0.45 ^{b, d}	2.16±0.47 ^{c, e}
Itraconazole AUC _{0–8} (ng·h/ml)	–	1843±488	–	733±312 ^f
Hydroxyitraconazole AUC _{0–8} (ng·h/ml)	–	4868±1137	–	2790±1074 ^f
Hydroxyitraconazole to Itraconazole AUC _{0–8} ratio	–	2.7±0.3	–	3.9±0.6 ^f
Gemfibrozil AUC _{0–8} (µg·h/ml)	–	–	105.3±30.4	115.0±37.4

Values shown as means ± SD; $t_{\max}$ data as median (range); Baseline concentration, fasting concentration on day 3 before repaglinide administration
Bonferroni adjusted p values:

^a $p<0.05$, ^b $p<0.01$, ^c $p<0.001$ versus placebo phase

^d $p<0.05$, ^e $p<0.01$, ^f $p<0.001$ versus itraconazole phase

^g $p<0.05$, ^h $p<0.01$, ⁱ $p<0.001$ versus gemfibrozil phase

Pharmacokinetics. Repaglinide pharmacokinetics were characterised by peak concentration in plasma ($C_{\max}$), time to $C_{\max}$ ($t_{\max}$), concentration at 7 h (C_7), AUC from time zero to 7 h (AUC_{0–7}) or infinity (AUC), and elimination half-life ($t_{1/2}$). The pharmacokinetics of M1 were characterised by $C_{\max}$, $t_{\max}$, and AUC_{0–7}. Gemfibrozil, itraconazole, and hydroxyitraconazole pharmacokinetics were characterised by AUC_{0–8}. The variables were calculated as described previously [6].

Pharmacodynamics. Repaglinide pharmacodynamics were characterised by blood glucose, serum insulin, and C-peptide concentrations, their mean concentrations calculated by dividing AUC by the corresponding time interval. Their baseline concentrations, minimum concentrations, and C_7 were taken from original data.

Statistics. Results are expressed as mean values ± SD (± SEM for clarity in the figure). Statistical comparisons between phases were made (after log-transformation of AUC and $C_{\max}$ values) with repeated measures ANOVA and a posteriori testing with the paired t-test with the Bonferroni correction. The $t_{\max}$ values were compared with Friedman's two-way ANOVA fol-

lowed by the Wilcoxon signed-rank test with the Bonferroni correction. The Pearson correlation coefficient was used to investigate relationships between pharmacokinetic and pharmacodynamic variables. The differences were considered statistically significant at a p value of less than 0.05.

Results

Repaglinide pharmacokinetics. In the gemfibrozil phase, repaglinide mean AUC was 812% (range 554–1504%, $p<0.001$) and the $C_{\max}$ 240% (range 169–608%, $p<0.001$) of those during the placebo phase (control) (Fig. 1A, Table 1). Gemfibrozil prolonged the $t_{1/2}$ of repaglinide from 1.3 to 3.7 h ($p<0.001$) and increased repaglinide C_7 28.6-fold (range 18.5- to 80.1-fold, $p<0.001$).

Itraconazole alone raised repaglinide AUC to 141% (range 105–193%, $p<0.001$) and the $C_{\max}$ to 147% (range 96–353%, $p<0.05$) of control. However, the

gemfibrozil-itraconazole combination raised repaglinide AUC to 1939% (range 1289–2465%, $p < 0.001$) and the $C_{\max}$ to 275% (range 216–504%, $p < 0.001$) of control and prolonged the $t_{1/2}$ to 6.1 h ($p < 0.001$). Repaglinide C_7 was increased 70.4-fold (range 42.9- to 119.2-fold, $p < 0.001$) by the gemfibrozil-itraconazole combination, compared with placebo. The increase in repaglinide AUC by itraconazole correlated with that by gemfibrozil ($r = 0.73$, $p < 0.01$).

Itraconazole alone and in combination with gemfibrozil markedly reduced the M1 to repaglinide AUC₀₋₇ ratio, whereas gemfibrozil alone had no significant effect (Fig. 1B, Table 1).

Pharmacodynamics. Gemfibrozil alone and with itraconazole enhanced and prolonged the effects of repaglinide on blood glucose, serum insulin, and C-peptide concentrations (Fig. 1C,D, Table 1). The blood glucose-lowering effect of repaglinide had almost subsided by 7 h during the placebo and itraconazole phases, but the effect was considerable for at least 7 h during the gemfibrozil, and in particular, the gemfibrozil-itraconazole phase. Two subjects required carbohydrate supplementation because of symptomatic hypoglycaemia during the gemfibrozil-itraconazole phase.

Gemfibrozil, itraconazole, and hydroxyitraconazole. The mean AUC₀₋₈ of itraconazole was 60% lower and that of hydroxyitraconazole 43% lower during the gemfibrozil-itraconazole phase than during the itraconazole phase ($p < 0.001$), but gemfibrozil pharmacokinetics were not changed by itraconazole (Table 1).

Discussion

This study shows that gemfibrozil greatly increases plasma concentrations of repaglinide and enhances and prolongs its blood glucose-lowering effect: this previously unrecognised interaction is most obviously clinically important. The gemfibrozil-itraconazole combination further increases the plasma concentrations and enhances the effects of repaglinide, although itraconazole alone has only minor effects. The greatest individual increases in the AUC of repaglinide by gemfibrozil and by the gemfibrozil-itraconazole combination were 15-fold and 25-fold, respectively. In these combinations repaglinide became a long-acting antidiabetic; repaglinide C_7 was increased 29-fold by gemfibrozil and 70-fold by the gemfibrozil-itraconazole combination. If not recognised, such interactions can result in severe and prolonged hypoglycaemia.

Because disturbances in insulin secretion and action are central to the pathogenesis of Type 2 diabetes mellitus, the pharmacodynamic response to repaglinide should be extrapolated with caution from healthy volunteers to patients with diabetes. However, the pharmacokinetics of repaglinide are similar among

healthy volunteers and patients with diabetes [1]. Thus, it is reasonable to assume that the pharmacokinetic interactions of repaglinide are similar in both groups. As the blood glucose-lowering effect of repaglinide is greater in healthy volunteers than in patients with diabetes, only one-half of the smallest tablet was given to prevent severe hypoglycaemia.

Repaglinide is eliminated by CYP2C8 and CYP3A4 to its major metabolites, an aromatic amine (M1, by CYP3A4) and a dicarboxylic acid (M2), and to a minor extent by direct glucuronidation [1, 2]. In our study, itraconazole markedly reduced the formation of M1, whereas gemfibrozil had no effect. Thus, itraconazole inhibits the CYP3A4-mediated metabolism of repaglinide, and gemfibrozil (which is not an inhibitor of CYP3A4) [7] inhibits the elimination via another pathway, probably CYP2C8 [3, 4]. In addition, inhibition of glucuronidation or drug transporter could contribute to gemfibrozil interactions [8]. The correlation between the interactions of repaglinide with gemfibrozil and itraconazole might be explained by coordinate transcriptional regulation of CYP2C8 and CYP3A4.

The extent of this gemfibrozil-repaglinide interaction strongly suggests that CYP2C8 is the principal enzyme responsible for eliminating repaglinide. Thus, also other inhibitors of CYP2C8 (e.g., trimethoprim) could interact with repaglinide. The interaction of repaglinide with inhibitors of CYP3A4 is rather small, as previously shown for clarithromycin [6]. However, concomitant use of repaglinide with drug-combinations inhibiting both CYP2C8 and CYP3A4 could be particularly hazardous.

This pharmacokinetic interaction between gemfibrozil and repaglinide is, as yet, the greatest reported for either drug. Gemfibrozil has raised the mean AUC of glimepiride 1.2-fold [9], that of simvastatin and lovastatin acids two to threefold [7, 10], and that of cerivastatin fivefold [4]. Cerivastatin (Lipobay) was withdrawn from the market, partly because of its potentially fatal interaction with gemfibrozil.

During the gemfibrozil-itraconazole phase, the itraconazole and hydroxyitraconazole AUC₀₋₈ values were markedly lower than during the itraconazole phase. This would be compatible with gemfibrozil displacing itraconazole and hydroxyitraconazole from plasma protein. Such an effect would enhance their clearances and reduce their plasma concentrations. An alternative explanation would be that gemfibrozil reduced the bioavailability of itraconazole.

In conclusion, gemfibrozil had a major pharmacokinetic interaction with repaglinide resulting in markedly enhanced and prolonged blood glucose-lowering effect. This interaction was further pronounced by the CYP3A4 inhibitor itraconazole. The concomitant use of gemfibrozil and repaglinide is best avoided. If the combination is considered necessary, the dosage of repaglinide should be greatly reduced and blood glucose concentrations carefully monitored, keeping in

mind that repaglinide is no longer a short-acting anti-diabetic.

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References

1. Hatorp V (2002) Clinical pharmacokinetics and pharmacodynamics of repaglinide. *Clin Pharmacokinet* 41:471–483
2. Bidstrup TB, Bjørnsdottir I, Thomsen MS, Hansen KT (2001) CYP2C8 and CYP3A4 are the principle enzymes involved in the in vitro biotransformation of the insulin secretagogue repaglinide. *Pharmacol Toxicol* 89 [Suppl 1]:65 (Abstract)
3. Wang JS, Neuvonen M, Wen X, Backman JT, Neuvonen PJ (2002) Gemfibrozil inhibits CYP2C8-mediated cerivastatin metabolism in human liver microsomes. *Drug Metab Dispos* 30:1352–1356
4. Backman JT, Kyrklund C, Neuvonen M, Neuvonen PJ (2002) Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther* 72:685–691
5. Olkkola KT, Backman JT, Neuvonen PJ (1994) Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther* 55:481–485
6. Niemi M, Neuvonen PJ, Kivistö KT (2001) The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 70:58–65
7. Backman JT, Kyrklund C, Kivistö KT, Wang JS, Neuvonen PJ (2000) Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 68:122–129
8. Prueksaritanont T, Zhao JJ, Ma B et al. (2002) Mechanistic studies on metabolic interactions between gemfibrozil and statins. *J Pharmacol Exp Ther* 301:1042–1051
9. Niemi M, Neuvonen PJ, Kivistö KT (2001) Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of glimepiride. *Clin Pharmacol Ther* 70:439–445
10. Kyrklund C, Backman JT, Kivistö KT, Neuvonen M, Laitila J, Neuvonen PJ (2001) Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 69:340–345