Dose-Dependent Interaction between Gemfibrozil and Repaglinide in Humans: Strong Inhibition of CYP2C8 with Subtherapeutic Gemfibrozil Doses

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ABSTRACT:

Gemfibrozil 1-O-β-glucuronide inactivates CYP2C8 irreversibly. We investigated the effect of gemfibrozil dose on CYP2C8 activity in humans using repaglinide as a probe drug. In a randomized, five-phase crossover study, 10 healthy volunteers ingested 0.25 mg of repaglinide 1 h after different doses of gemfibrozil or placebo. Concentrations of plasma repaglinide, gemfibrozil, their metabolites, and blood glucose were measured. A single gemfibrozil dose of 30, 100, 300, and 900 mg increased the area under the concentration-time curve of repaglinide 1.8-, 4.5-, 6.7-, and 8.3-fold ($P < 0.001$), and its peak concentration 1.4-, 1.7-, 2.1-, and 2.4-fold ($P < 0.05$), compared with placebo, respectively. Gemfibrozil pharmacokinetics was characterized by a slightly more than dose-proportional increase in the area under the curve of gemfibrozil and its glucuronide. The gemfibrozil-repaglinide interaction could be mainly explained by gemfibrozil 1-O-β-glucuronide concentration-dependent, mechanism-based inhibition of CYP2C8, with a minor contribution by competitive inhibition of organic anion-transporting polypeptide 1B1 at the highest gemfibrozil dose. The findings are consistent with ~50% inhibition of CYP2C8 already with a single 30-mg dose of gemfibrozil and >95% inhibition with 900 mg. In clinical drug-drug interaction studies, a single 900-mg dose of gemfibrozil can be used to achieve nearly complete inactivation of CYP2C8.

Introduction

CYP2C8 is one of the major drug-metabolizing cytochrome P450 (P450) forms, and it accounts for approximately 6% of the hepatic P450 content (Totah and Rettie, 2005; Lai et al., 2009). CYP2C8 can be inhibited in vitro by many commonly used drugs, e.g., gemfibrozil, montelukast, isoniazid, nortriptyline, amiodarone, verapamil, and trimethoprim (Polasek et al., 2004; Walsky et al., 2005a,b; Lai et al., 2009). The importance of CYP2C8-mediated drug interactions is increasing continuously, because the list of CYP2C8 substrates, and therefore the list of potential victim drugs of CYP2C8-mediated interactions, is increasing. To date, for example, paclitaxel, cerivastatin, lopamide, rosiglitazone, repaglinide, amiodarone, amodiaquine, and montelukast have been recognized as CYP2C8 substrates (Rahman et al., 1994; Ohyama et al., 2000; Backman et al., 2002; Wang et al., 2002; Niemi et al., 2003a; Kim et al., 2004; Jaakkola et al., 2005; Kajosaari et al., 2005a; Totah and Rettie, 2005; Niemi et al., 2006; Lai et al., 2009; Karonen et al., 2010; Filppula et al., 2011). When developing new therapeutic agents, it is important, among other things, to assess whether their metabolism is dependent on CYP2C8 (Huang et al., 2007, 2008).

Repaglinide is a short-acting meglitinide class anti-diabetic drug, which has been recommended as a probe substrate for studying CYP2C8 activity (U.S. Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdfFDA). The formations of the repaglinide main metabolites M2 and M4 are mainly mediated by CYP2C8, whereas M1 is mainly formed by CYP3A4 (Bidstrup et al., 2003; Kajosaari et al., 2005a,b). The changes in pharmacokinetic variables of parent repaglinide and its metabolites reflect changes in CYP2C8 activity (Niemi et al., 2003a,b, 2004; Backman et al., 2009; Honkalammi et al., 2011). In addition, genetic variability in the

ABBREVIATIONS: P450, cytochrome P450; AUC, area under the concentration-time curve; $f_{\text{unbound}}$, the hepatocyte (unbound) to plasma (total) concentration ratio; $C_{\text{max}}$, peak concentration; $f_{\text{dose/cytP450}}$, the fraction of repaglinide dose metabolized by CYP2C8; $f_{\text{dose/OATP1B1}}$, fraction of dose transported by OATP1B1; $K_m$, the first-order degradation rate constant; $K_i$, the inhibitor concentration that supports half the maximal rate of enzyme inactivation; $K_{\text{act}}$, maximal rate of enzyme inactivation; $SLOCO1B1$, solute carrier organic anion transporter family, member 1B1 gene encoding for OATP1B1; $T_{\text{max}}$, time to peak concentration; CV, coefficient of variation; AUC/CYP2C8, fold change in total area under the concentration-time curve of repaglinide; $C_{\text{avg,10 h}}$, average plasma concentration calculated from AUC$_{0-10\text{h}}$; $K_{\text{el}}$, elimination rate constant; AUC$_{0-3\text{h}}$, area under the plasma concentration-time curve from time 0 to 3 h; AUC$_{0-9\text{h}}$, area under the plasma concentration-time curve from time 0 to 9 h.
Metabolite, gemfibrozil 1-glucuronide (Wang et al., 2002; Shitara et al., 2004). Recent studies using repaglinide as a CYP2C8 probe substrate have shown that the inactivation of CYP2C8 occurs rapidly in humans (Honkalammi et al., 2011) and that the recovery of repaglinide following administration of gemfibrozil (Backman et al., 2002). In addition, gemfibrozil and its glucuronide may competitively inhibit OATP1B1 and therefore interfere with repaglinide pharmacokinetics (Shitara et al., 2004). Recent studies using repaglinide as a CYP2C8 probe substrate have shown that the inactivation of CYP2C8 occurs rapidly in humans (Honkalammi et al., 2011) and that the recovery of CYP2C8 takes place slowly after cessation of gemfibrozil administration (Tornio et al., 2008; Backman et al., 2009). These findings are consistent with the mechanism-based nature of the inhibitory effect. However, the dependence of CYP2C8 inactivation on the dose of gemfibrozil is not known. This information would be particularly relevant for the selection of the gemfibrozil dose when it is used as a CYP2C8 probe inhibitor.

The aim of the present study was to investigate the dose dependence of the inactivation of CYP2C8 by gemfibrozil using repaglinide as a CYP2C8-probe drug and to apply enzyme and transporter inhibition models to the obtained in vivo data, to better understand the concentration dependence and mechanism of the observed interaction. We used a study design in which 10 healthy volunteers were given a single dose of repaglinide after an oral dose of 30, 100, 300, or 900 mg of gemfibrozil or placebo in a double-blind crossover study of five phases.

Materials and Methods

Subjects. Ten healthy volunteers (one female and nine males; age, 20–26 years; body mass index, 21–27 kg/m²) participated in the study after giving written informed consent (Table 1), and their health was ascertained by medical history, physical examination, and routine laboratory tests before entering the study. None of the volunteers were smokers or used any continuous medication. The sample size was estimated to be sufficient to detect a 30% change in the AUC<sub>0-∞</sub> of repaglinide with a power of 80% (α level, 5%).

Study Design. The study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District and by the National Agency for Medicines. A randomized crossover study with five phases and a washout period of 2 weeks between phases was carried out. All subjects completed all five phases of the study. On the study day, a single oral dose of 0.25 mg of repaglinide (half of a 0.5-mg tablet of NovoNorm; Novo Nordisk, Bagsværd, Denmark) was administered with 150 ml of water at 9:00 AM after an overnight fast and 1 h after a single 30-, 100-, 300-, or 900-mg dose of gemfibrozil or placebo. Gemfibrozil and placebo capsules were prepared and analyzed using methods described in the European Pharmacopoeia by the Helsinki University Central Hospital Pharmacy. Placebo capsules contained microcrystallized cellulose (Orion Pharma, Espoo, Finland), and gemfibrozil capsules contained pulverized gemfibrozil (prepared from 600-mg Lopid tablets; Gödecke, Freiburg, Germany) and microcrystallized cellulose, as appropriate. The gemfibrozil content of the capsules was measured using the liquid chromatography-tandem mass spectrometry system described below.

Food intake was identical in all phases: a standardized light breakfast 15 min after repaglinide administration, snacks after 1 and 2 h, a warm meal after 3 h, and snacks after 7 and 9 h. Additional carbohydrates, glucose solution for intravenous use, and glucagon for intramuscular use were available for use in case of severe hypoglycemia.

Sampling. Timed blood samples (4 or 9 ml each) were drawn from a cannulated forearm vein 60, 30, and 5 min before and at 15, 30, 45, 60, 80, and 100 min and 2, 2.5, 3, 4, 5, 7, and 9 h after the administration of repaglinide. Blood samples were taken into EDTA-containing tubes. Blood glucose concentrations were measured immediately after sampling using a Precision Exceed device (Abbott Diabetes Care Ltd., Witney Oxon, UK). Plasma was separated within 30 min and stored at −70°C until analysis.

Determination of Drug Concentrations. Concentrations of repaglinide and its metabolites M1, M2, and M4 were measured in plasma samples by use of an API 3000 liquid chromatography-tandem mass spectrometry system (MDS Sciex, Toronto, ON, Canada), as described previously (Tornio et al., 2008; Backman et al., 2009). The limit of quantification for repaglinide was 0.01 ng/ml, and interday coefficient of variation (CV) were 4.6% at 0.1 ng/ml, 2.6% at 2.0 ng/ml, and 2.3% at 20 ng/ml (n = 6). The limit of quantification for repaglinide M1 and M2 was 0.05 ng/ml, and interday CV were 14.7 and 8.9% at 0.1 ng/ml and 7.5 and 11.5% at 2.0 ng/ml for M1 and M2, respectively.

### Table 1

Characteristics of the subjects, the parameter values from regression analysis based on a mechanism-based CYP2C8 inhibition model, and the observed maximum fold increase in repaglinide AUC<sub>0-∞</sub> when 0.25 mg of repaglinide was given to each subject 1 h after a single 30-, 100-, 300-, or 900-mg dose of gemfibrozil, compared with placebo.

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Mean ± S.D. 23 ± 2 73 ± 10 23 ± 2 0.285 ± 0.149 0.887 ± 0.024 8.4 ± 1.9

BMI, body mass index.
(n = 6). Because an authentic metabolite standard for M4 was not available, M4 concentrations are given in arbitrary units (units per milliliter) relative to the ratio of the peak height of M4 to that of the internal standard in the chromatogram. The limit of quantification for M4 was based on a signal-to-noise ratio of more than 10:1. The plasma concentrations of gemfibrozil and gemfibrozil 1-O-β-glucuronide were determined by use of the API 2000 liquid chromatography-tandem mass spectrometry system (MDS Sciex) (Backman et al., 2009; Honkalanni et al., 2011). Gemfibrozil-d6 and gemfibrozil 1-O-β-glucuronide-d6 served as internal standards. The limits of quantification for gemfibrozil and gemfibrozil 1-O-β-glucuronide were 2.5 ng/ml, and interday CV were 4.4 to 8.7 and 3.0 to 7.0% at relevant plasma concentrations, respectively.

**Pharmacokinetics.** The pharmacokinetics of repaglinide and its metabolites M1, M2, and M4 were characterized by Cmax, time to Cmax (Tmax), areas under the plasma concentration-time curve (AUC0–9 h and AUC0–12 h for M4), and elimination half-life (t1/2), calculated by noncompartmental analysis using the MK-Model (version 5.0; Biosoft, Cambridge, UK). The terminal log-linear part of each concentration-time curve was identified visually. The elimination rate constant (k) was determined by linear regression analysis of the log-linear part of the plasma concentration-time curve. The t1/2 was calculated by the equation t1/2 = ln2/k. The AUC values were calculated by use of the linear trapezoidal rule for the rising phase of the plasma 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. The pharmacokinetics of gemfibrozil and gemfibrozil 1-O-β-glucuronide were characterized by concentration at 1 h after dose (C1h), Cmax, Tmax, t1/2, and AUC.

**Pharmacodynamics.** The pharmacodynamics of repaglinide were characterized by baseline blood glucose concentration, minimum blood glucose concentration, and mean blood glucose concentration during the study day, from 0 to 9 h after repaglinide intake.

**Genotyping.** For genotyping, a 12-ml EDTA blood sample was drawn from each subject and stored at −20°C. Genomic DNA was extracted with standard methods (Qiaamp DNA Blood Mini kit; QIAGEN, Hilden, Germany). The subjects were genotyped for the CYP2C8*3 (c.416G>A and c.1196A>G) and CYP2C8*4 (c.792C>G) alleles and the SLCO1B1 c.388A>G and c.521T>C single-nucleotide polymorphisms, defining the SLCO1B1*1B (GT), *5 (AC), and *15 (GC) haplotypes (Kalliokoski and Niemi, 2009), with TaqMan genotyping assays on a 7300 Real-Time PCR system (Applied Biosystems, Foster City, CA) (Pasanen et al., 2006).

**Statistical Analysis.** The results are expressed as means ± S.D. in the text, tables, and figures, unless indicated otherwise. The pharmacokinetic and pharmacodynamic variables between the study phases were compared by the paired t test. To avoid false-negative conclusions and because the direction of the interaction has been documented previously, no Bonferroni correction for multiple comparisons was applied, and differences were considered statistically significant at P < 0.05. The Tmax data were compared using the Wilcoxon signed-rank test.

The dose-proportionality of gemfibrozil pharmacokinetics was estimated by regression analysis with the power model approach using a logarithmically transformed form of the equation $AUC_{\text{tot}} = c^* \cdot \text{dose}^{0.5}$ after logarithmic transformation of the AUC data, where statistically significant deviation of the term $\beta$ from unity indicates nonlinearity.

To characterize the dose dependence of the gemfibrozil-repaglinide interaction, we applied several static enzyme and transporter inhibition models to the relationship between the plasma concentrations of gemfibrozil or its 1-O-β-glucuronide and the increase in the AUC of repaglinide, with the following assumptions and simplifications.

1. The increment in repaglinide AUC was due to a single mechanism only, i.e., either irreversible mechanism-based inactivation of hepatic CYP2C8 or competitive inhibition of OATP1B1 by gemfibrozil 1-O-β-glucuronide, or competitive inhibition of hepatic CYP2C8 or OATP1B1 by gemfibrozil, and no other kind of changes in the activity of relevant enzymes or transporters was involved.

2. For mechanism-based inhibition, the conditions were assumed to approximate static “steady-state” conditions, where the average (or peak) plasma concentration of gemfibrozil 1-O-β-glucuronide during the study day (0–10 h after gemfibrozil intake) reflects its steady-state concentration in hepatocytes and repaglinide AUC reflects the average CYP2C8 activity in hepatocytes.

3. For all models, it was assumed that all possible parallel metabolism or transport/elimination pathways can be described as first-order processes and that the gemfibrozil treatment has no effect on such parallel processes other than CYP2C8 and OATP1B1.

For mechanism-based inhibition, the fold increase in repaglinide AUC caused by the different gemfibrozil doses in the 10 subjects was expressed using the following equation:

$$AUC_{\text{tot}} = 1/(f_{\text{act}} \cdot C_{\text{p,tot}} \cdot C_{\text{avg,10 hr}}),$$

where $f_{\text{act}}$ is the maximal rate of CYP2C8 inactivation, $C_{\text{p,tot}}$ is the first-order degradation rate constant of CYP2C8, $C_{\text{avg,10 hr}}$ is the hepatocyte (unbound) to plasma (total) concentration ratio and $C_{\text{p,tot}}$ is the hepatocyte concentration at 1 h.
C_{\text{avg},\text{i},h}$ is the average plasma concentration of gemfibrozil 1-\text{O}-\beta-glucuronide calculated from its AUC_{0–10\,h}. The $C_{\text{avg},\text{i},h}$ and $\text{f}_{\text{OATP1B1}}$ were left as the unknown parameters to be estimated by nonlinear regression analysis. For this model, fixed values of the $k_{\text{max}}$ (0.21 min\(^{-1}\)) and $K_{i}$ (20 \mu M) were taken from a previous in vitro study (Ogilvie et al., 2006), and the $k_{r}$ (0.000558 min\(^{-1}\)) was estimated from previous in vivo study (Backman et al., 2009). Because this approach was found to best explain the interaction, the model was also applied to each subject individually.

To evaluate whether competitive inhibition of CYP2C8 or OATP1B1 by parent gemfibrozil or competitive inhibition of OATP1B1 by gemfibrozil 1-\text{O}-\beta-glucuronide could explain the observed drug interaction, the data were modeled using the competitive-inhibition-based equations $\text{AUC}/\text{AUC}_{0} = 1/(\text{f}_{\text{OATP1B1}}(1 + [\text{I}]_{h}/K_{i}) + (1 - \text{f}_{\text{OATP1B1}}))$ for inhibition of CYP2C8 and $\text{AUC}/\text{AUC}_{0} = 1/(\text{f}_{\text{OATP1B1}}(1 + [\text{I}]_{h}/K_{i}) + (1 - \text{f}_{\text{OATP1B1}}))$ for inhibition of OATP1B1, where $[\text{I}]_{h}$ is calculated as above for either gemfibrozil or gemfibrozil 1-\text{O}-\beta-glucuronide, $K_{i}$ is the in vitro competitive inhibition constant of the inhibitor, and $\text{f}_{\text{OATP1B1}}$ is the fraction transported by OATP1B1 (determines the maximal fold increase in repaglinide AUC, obtained with complete inhibition of OATP1B1). For this analysis, the $K_{i}$ of gemfibrozil for CYP2C8 (36.4 \mu M) was taken from Wang et al. (2002), using correction for microsomal binding of gemfibrozil as described by Hinton et al. (2008), and the $K_{i}$ values of gemfibrozil and gemfibrozil 1-\text{O}-\beta-glucuronide for inhibition of OATP1B1 were taken as IC_{50}/2, based on the IC_{50} values of 7.4 \mu M for gemfibrozil and 24.3 \mu M for gemfibrozil 1-\text{O}-\beta-glucuronide (Shitara et al., 2004; Hinton et al., 2008). For all the above models, the $[\text{I}]_{h}$ was alternatively expressed as $[\text{I}]_{h} = \text{C_{avg},\text{i},h}/K_{i}$.

Because the in vitro inhibitory potencies and plasma unbound fractions of gemfibrozil and gemfibrozil 1-\text{O}-\beta-glucuronide suggested that inhibition of OATP1B1 by gemfibrozil 1-\text{O}-\beta-glucuronide is the second most important mechanism for the increase in repaglinide AUC, a combined reversible OATP1B1 inhibition and time-dependent CYP2C8 inhibition model was applied, using the following equation: $\text{AUC}/\text{AUC}_{0} = 1/(\text{f}_{\text{OATP1B1}}(1 + ([\text{I}]_{h}/K_{i}) + (1 - \text{f}_{\text{OATP1B1}})) × 1/[[\text{f}_{\text{OATP1B1}}(1 + ([\text{I}]_{h}/K_{i}) + (1 - \text{f}_{\text{OATP1B1}}))]/\text{K}_{i}$ for the interaction.

Because the in vitro inhibitory potencies and plasma unbound fractions of gemfibrozil and gemfibrozil 1-\text{O}-\beta-glucuronide seems to be very weak (Ogilvie et al., 2006), competitive inhibition of CYP2C8 by gemfibrozil 1-\text{O}-\beta-glucuronide was not considered as a relevant mechanism for the interaction.

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Because the in vitro inhibitory potencies and plasma unbound fractions of gemfibrozil and gemfibrozil 1-\text{O}-\beta-glucuronide seems to be very weak (Ogilvie et al., 2006), competitive inhibition of CYP2C8 by gemfibrozil 1-\text{O}-\beta-glucuronide was not considered as a relevant mechanism for the interaction.
Results

Pharmacokinetic Variables of Parent Repaglinide. Escalating doses of gemfibrozil had a dose-dependent effect on the pharmacokinetics of repaglinide. The mean AUC<sub>0-3h</sub> of repaglinide was increased 1.8-, 4.5-, 6.7-, or 8.3-fold by a single gemfibrozil dose of 30, 100, 300, or 900 mg, respectively (P < 0.001; Fig. 1; Table 2). In addition, the C<sub>max</sub> of repaglinide was increased after all gemfibrozil doses used, i.e., 1.4-, 1.7-, 2.1-, and 2.4-fold, respectively (P < 0.05; Table 2). The increase in the t<sub>1/2</sub> of repaglinide reached a 2.0-fold prolongation (P < 0.001) with the 900-mg gemfibrozil dose, whereas shorter but statistically significant prolongations were observed with the smaller gemfibrozil doses (P < 0.05; Fig. 1; Table 2).

Pharmacokinetic Variables of Repaglinide Metabolites. The 900-mg dose of gemfibrozil abolished the formation of the CYP2C8-dependent repaglinide metabolite M4 in almost all subjects, and the exact pharmacokinetic variables for M4 in this phase could not be calculated (Fig. 2; Table 2). With 100- and 300-mg gemfibrozil doses, dose-dependent decreases in the C<sub>max</sub> AUC<sub>0-3h</sub> and AUC<sub>0-9h</sub> of M4 were seen. The smallest gemfibrozil dose (30 mg) decreased the M4:repaglinide AUC<sub>0-3h</sub> ratio (P < 0.005; Table 2) but had no effect on the other pharmacokinetic variables of M4.

The M2:repaglinide AUC<sub>0-9h</sub> ratio was decreased by 40 to 80% by the different gemfibrozil doses (P < 0.005). With gemfibrozil doses of 100 mg and higher, the C<sub>max</sub> of M2 was decreased and t<sub>1/2</sub> was prolonged (Table 2). In parallel with the prolonged t<sub>1/2</sub>, small (<1.6-fold) increases in the AUC<sub>0-3h</sub> of M2 were observed at the highest gemfibrozil doses.

With the doses of 100, 300, and 900 mg, gemfibrozil dose-dependently increased the AUC<sub>0-3h</sub> of M1 and prolonged its t<sub>1/2</sub>, whereas there were no changes in these variables with the 30-mg gemfibrozil dose (Table 2). The metabolite M1 to repaglinide AUC ratios were significantly decreased in all gemfibrozil phases compared with the control (P < 0.005).

Pharmacodynamics. The minimum blood glucose concentration was significantly smaller when repaglinide was given after a gemfibrozil dose of 100, 300, or 900 mg (P < 0.05) than when it was given in the control phase (Fig. 1; Table 3). The mean blood glucose concentration 0 to 3 and 0 to 9 h after repaglinide intake was significantly decreased by the 300- and 900-mg gemfibrozil doses only (P < 0.005 and P < 0.05, respectively).

Gemfibrozil and Gemfibrozil 1-O-β-Glucuronide Pharmacokinetics. There was a more than 30-fold difference in the mean plasma concentrations of gemfibrozil and gemfibrozil 1-O-β-glucuronide between the 30- and 900-mg doses of gemfibrozil (Fig. 3). The AUC values of gemfibrozil and its glucuronide increased slightly more than

TABLE 3
Blood glucose levels in 10 healthy volunteers after a single oral dose of 0.25 mg of repaglinide, which was administered 1 h after placebo or a single oral dose of 30, 100, 300, or 900 mg of gemfibrozil

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Gemfibrozil Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30 mg</td>
</tr>
<tr>
<td>Baseline concentration (mmol/l)</td>
<td>5.1 ± 0.6</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td>Minimum concentration (mmol/l)</td>
<td>3.6 ± 0.4</td>
<td>3.5 ± 0.6</td>
</tr>
<tr>
<td>Mean concentration from 0 to 3 h (mmol/l)</td>
<td>4.9 ± 0.5</td>
<td>4.7 ± 0.5</td>
</tr>
<tr>
<td>Mean concentration from 0 to 9 h (mmol/l)</td>
<td>4.8 ± 0.4</td>
<td>4.8 ± 0.4</td>
</tr>
</tbody>
</table>

* P < 0.05 vs. control; ** P < 0.005 vs. control; *** P < 0.001 vs. control; † P < 0.05 vs. 30 mg; †† P < 0.005 vs. 30 mg; ‡ P < 0.05 vs. 300 mg.
dose-proportionally (Fig. 3; Table 4). The nonlinearity was slightly greater for the glucuronide than for the parent gemfibrozil, resulting in a dose-dependent increase in the glucuronide/gemfibrozil AUC ratio (Table 4).

Relationship between the Plasma Concentrations of Gemfibrozil or its 1-0-Glucuronide and the Fold Increase in the AUC of Repaglinide. A static model assuming that mechanism-based inhibition of CYP2C8 by gemfibrozil 1-0-glucuronide is the sole explanation for the interaction described the relationship between the extent of the interaction (repaglinide AUC/AUC0) and the Cavg,10h of gemfibrozil 1-0-glucuronide after the different gemfibrozil doses in the entire population (r^2 = 0.79). With this nonlinear regression model, the unknown parameters, i.e., the fraction of repaglinide dose metabolized by CYP2C8 (f_m,CYP2C8) and ratio of unbound hepatocyte concentration to total plasma concentration (C_{h,u}/C_{p,tot}) of gemfibrozil 1-0-glucuronide were estimated at 89% and 0.24, respectively (data not shown). The individual model-based estimates for the f_m,CYP2C8 of repaglinide and the C_{h,u}/C_{p,tot} of gemfibrozil 1-0-glucuronide averaged 89 ± 2% and 0.28 ± 0.15, respectively (Fig. 4; Table 1).

**TABLE 4**

Pharmacokinetic variables of gemfibrozil and gemfibrozil 1-0-glucuronide in 10 healthy volunteers after a single dose of 30, 100, 300, or 900 mg of gemfibrozil, which was taken 1 h before administration of repaglinide

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 mg</th>
<th>100 mg</th>
<th>300 mg</th>
<th>900 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{1h} (µg/ml)</td>
<td>1.0 ± 0.5</td>
<td>3.7 ± 2.0</td>
<td>8.5 ± 5.7</td>
<td>32.9 ± 8.8</td>
</tr>
<tr>
<td>C_{max} (µg/ml)</td>
<td>1.4 ± 0.4</td>
<td>4.8 ± 0.7</td>
<td>15.2 ± 4.5</td>
<td>48.0 ± 10.1</td>
</tr>
<tr>
<td>T_{max} (min)</td>
<td>60 (30–105)</td>
<td>67.5 (60–105)</td>
<td>97.5 (60–120)^*</td>
<td>90 (75–105)^*</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>1.9 ± 0.4</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.5</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>AUC_{0–10h} (µg · h/ml)</td>
<td>2.0 ± 0.4</td>
<td>8.8 ± 1.9</td>
<td>30.6 ± 7.2</td>
<td>125.4 ± 25.8</td>
</tr>
<tr>
<td>AUC_{0–24h} (µg · h/ml)</td>
<td>2.1 ± 0.4</td>
<td>9.0 ± 2.0</td>
<td>31.3 ± 7.1</td>
<td>128.5 ± 26.6</td>
</tr>
<tr>
<td>Gemfibrozil-1-0-glucuronide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{1h} (µg/ml)</td>
<td>0.3 ± 0.2</td>
<td>1.3 ± 0.9</td>
<td>2.4 ± 1.7</td>
<td>9.0 ± 2.5</td>
</tr>
<tr>
<td>C_{max} (µg/ml)</td>
<td>0.5 ± 0.1</td>
<td>2.5 ± 0.4</td>
<td>7.8 ± 1.4</td>
<td>21.6 ± 4.5</td>
</tr>
<tr>
<td>T_{max} (min)</td>
<td>67.5 (50–120)</td>
<td>90 (75–140)</td>
<td>130 (90–140)^*</td>
<td>140 (90–160)^*</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>1.8 ± 0.4</td>
<td>1.7 ± 0.3</td>
<td>1.7 ± 0.6</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>AUC_{0–10h} (µg · h/ml)</td>
<td>0.9 ± 0.2</td>
<td>5.7 ± 1.1</td>
<td>21.9 ± 4.1</td>
<td>86.7 ± 18.6</td>
</tr>
<tr>
<td>AUC_{0–24h} (µg · h/ml)</td>
<td>0.95 ± 0.17</td>
<td>5.8 ± 1.2</td>
<td>22.6 ± 4.2</td>
<td>91.5 ± 19.9</td>
</tr>
<tr>
<td>Glucuronide/gemfibrozil AUC_{0–24h} ratio</td>
<td>0.47 ± 0.08</td>
<td>0.66 ± 0.12**</td>
<td>0.74 ± 0.15**</td>
<td>0.73 ± 0.17**</td>
</tr>
</tbody>
</table>

C_{1h}, plasma concentration 1 h after gemfibrozil intake (i.e., at the time of repaglinide administration); AUC_{0–10h}, area under the plasma concentration-time curve from time 0 to 10 h; AUC_{0–24h}, area under the plasma concentration-time curve from time 0 to infinity; C_{avg,10h}, area under the plasma concentration-time curve from time 0 to 10 h.

* P < 0.05 vs. 30 mg; ** P < 0.001 vs. 30 mg; † P < 0.05 vs. 100 mg.
AUCi/AUCc ratio when 50% of CYP2C8 is inactivated, and the dashed-dotted lines represent the AUCi/AUCc ratio when 90% of CYP2C8 is inactivated. The curved lines represent the best-fit functions, the dotted lines represent the AUCavg,10 h of gemfibrozil 1-O-glucuronide has inhibited CYP2C8 and the unbound plasma fraction of gemfibrozil in plasma, 0.65% (Shitara et al., 2004). For competitive inhibition of OATP1B1 by gemfibrozil 1-O-β-glucuronide, the Cavg,10 h of gemfibrozil 1-O-β-glucuronide (with the Cavg,10 h of gemfibrozil 1-O-β-glucuronide has inhibited CYP2C8 and the unbound plasma Cmax of gemfibrozil 1-O-β-glucuronide for inhibition of OATP1B1 (r² = 0.81). With this model, the estimated fM,CYP2C8 and fOATP1B1 were 0.37, 84%, and 94%, respectively (Fig. 5).

**Genotypes.** One subject was homozygous and one was heterozygous for the CYP2C8*3 allele, associated with increased repaglinide metabolism (Niemi et al., 2003b), whereas the other subjects had the CYP2C8*1/*1 genotype. Four subjects were heterozygous for the SLCO1B1*1B allele, associated with increased OATP1B1 activity (Kalliokoski et al., 2008b), and four were heterozygous for the SLCO1B1*15 allele, associated with reduced OATP1B1 activity (Kalliokoski et al., 2008c), with one subject being compound heterozygous for both variants (SLCO1B1*1B/*15 genotype). No differences in the extent of the interaction between the SLCO1B1 genotypes could be seen, but the observed extent of the interaction and the mechanism-based CYP2C8 inhibition model-derived fM,CYP2C8 of repaglinide were greatest in carriers of the CYP2C8*3 allele (P = 0.0007 and P = 0.003, respectively; Figs. 4 and 5).

**Discussion**

In this study, gemfibrozil dose-dependently increased the AUC of repaglinide and inhibited its metabolism in humans. Already, 30 mg of gemfibrozil increased repaglinide AUC nearly 2-fold. An average 4.5- and 6.7-fold AUC increase was reached with the 100- and 300-mg doses, indicating that the dose dependence was steep at the low-dose range. With the highest 900-mg gemfibrozil dose, the M4 metabolite of repaglinide was completely abolished, and the AUC of repaglinide was increased 8.3-fold, i.e., even more than previously with repeated doses of 600 mg of gemfibrozil twice daily (Niemi et al., 2003a; Kalliokoski et al., 2008a; Tornio et al., 2008; Backman et al., 2009). Our regression models were consistent with over 90% inhibition of CYP2C8 by gemfibrozil at this dose level in all subjects and approximately 50% inhibition already with the 30-mg dose.

The metabolism of repaglinide occurs in the hepatocytes by CYP3A4 and CYP2C8 (Bidstrup et al., 2003; Kajosaari et al., 2005a,b). The uptake transporter OATP1B1 is involved in the transport of repaglinide from blood to hepatocytes (Niemi et al., 2005; Kalliokoski et al., 2008a,b,c). Although CYP2C8 seems to be more important than CYP3A4 in vivo (Niemi et al., 2003a), the exact contributions of CYP2C8 and CYP3A4 to repaglinide metabolism are not known. The main mechanism of the gemfibrozil-repaglinide interaction is thought to be mechanism-based inactivation of CYP2C8 by gemfibrozil 1-O-β-glucuronide (Ogilvie et al., 2006; Baer et al., 2009). In vitro, gemfibrozil 1-O-β-glucuronide has inhibited CYP2C8 with a $k_{inact}$ of 0.21 min⁻¹ and a $K_i$ of 20 or 52 μM, depending on the microsomal protein concentration (0.1 or 1.0 mg/ml) used (Ogilvie et
The inactivation of CYP2C8 occurs rapidly in vivo, reaching strong inhibition within 1 to 3 h after a single 600-mg gemfibrozil dose (Honkalammi et al., 2011), and is long persisting, consistent with an in vivo CYP2C8 turnover half-life of approximately 22 h (Backman et al., 2009).

Gemfibrozil 1-O-β-glucuronide has also inhibited OATP1B1 activity in vitro, with an IC_{50} of 24.3 μM (Shitara et al., 2004). Moreover, parent gemfibrozil has inhibited CYP2C8 competitively with a protein binding-corrected K_i of 36.4 μM (Wang et al., 2002; Hinton et al., 2008) and OATP1B1 with an IC_{50} of 7.4 to 25 μM (Ho et al., 2006; Hinton et al., 2008).

We applied enzyme/transporter inhibitory models to explain the relationship between plasma concentrations of gemfibrozil or its 1-O-β-glucuronide and the increase in repaglinide AUC. With the models where mechanism-based inactivation of CYP2C8 by gemfibrozil 1-O-β-glucuronide was the main explanation for the interaction, we estimated that the unbound concentration of the glucuronide at the enzyme site in hepatocytes is lower than the total concentration of gemfibrozil 1-O-β-glucuronide in plasma (Shitara et al., 2004). Given that the glucuronide may accumulate in hepatocytes (Sallustio et al., 1996) and its peak concentrations are 2 to 5 times higher than its average plasma concentrations, our findings indicate that the mechanism-based CYP2C8 inhibitory effect is sufficiently strong to explain the majority of the interaction between gemfibrozil and repaglinide. With the competitive inhibition models, the estimated C_{u,p}/C_{p,tot} ratios of gemfibrozil and its glucuronide were 500 to 10,000 times higher than the respective plasma unbound fractions, indicating that their competitive CYP2C8 and OATP1B1 inhibitory effects cannot alone explain the increases in the AUC of repaglinide. Because a competitive OATP1B1 inhibition has previously been suggested to contribute to the interactions caused by gemfibrozil, it was incorporated into a model with mechanism-based inactivation. This model verified the crucial role of CYP2C8 inactivation by gemfibrozil 1-O-β-glucuronide in the interaction and suggested that inhibition of OATP1B1 is involved in the interaction mainly at gemfibrozil doses exceeding 300 mg and does not exceed 50% at clinically used gemfibrozil doses.

The combined CYP2C8 inactivation and OATP1B1 inhibition model resulted in an estimated “average” fraction of repaglinide dose metabolized by CYP2C8 of 84% and fraction transported by OATP1B1 of 94%. The estimated contribution of CYP2C8 is consistent with in vivo studies on interactions of repaglinide with CYP2C8 inhibitors (Niemi et al., 2003a; Backman et al., 2009), but higher than that suggested on the basis of in vitro studies (Bidstrup et al., 2003; Kajosaari et al., 2005a). Unfortunately, individual estimates of the f_{in,CYP2C8} of repaglinide could only be obtained with the mechanism-based CYP2C8 inhibition model (without OATP1B1). It is noteworthy that the individual f_{in,CYP2C8} values of repaglinide and the extent of the interaction were greatest in the two carriers of the CYP2C8*3 allele. Although the number of subjects in the present study was too small to draw any definitive conclusions, this finding is consistent with previous studies in which CYP2C8*3 was associated with increased clearance of repaglinide (Niemi et al., 2003b, 2005) and argues against the lack of association reported in other studies (Bidstrup et al., 2006; Tomalik-Scharte et al., 2011). The estimated f_{i,OATP1B1} of repaglinide is also in line with previous pharmacogenetic studies. There are genotypes with increased or decreased OATP1B1 activity, and the differences in the AUC of repaglinide between the extreme genotypes are approximately 3-fold (Niemi et al., 2005; Kalliokoski et al., 2008a,b,c).
The AUC values of gemfibrozil and gemfibrozil 1-O-β-glucuronide increased slightly more than dose-proportionally (Fig. 3). The non-linearity is apparently not clinically significant, because it required a 30-fold gemfibrozil dose range. Yet, it may indicate some degree of saturation of transporter- or enzyme-mediated elimination of gemfibrozil or its glucuronide.

The fold increase in repaglinide AUC approached a maximum with the 900-mg gemfibrozil dose (Fig. 4). This indicates that repaglinide metabolism was completely shifted to alternative routes, i.e., CYP2C8 was almost completely inactivated. Accordingly, the relative contribution of the CYP3A4-mediated metabolism of repaglinide, e.g., formation of M1 (Fig. 2), increased along with increasing doses of gemfibrozil and increasing concentrations of its 1-O-β-glucuronide. This explains why concomitant administration of gemfibrozil and the CYP3A4 inhibitor itraconazole has increased the AUC of repaglinide up to 19-fold, i.e., much more than did either of them alone (Niemi et al., 2003a).

The enzyme/transporter inhibition models including mechanism-based CYP2C8 inhibition were consistent with at least 50% inhibition of CYP2C8 with the 30-mg gemfibrozil dose, 75% inhibition at the 100-mg dose, 90% inhibition at the 300-mg dose, and over 95% inhibition at the 900-mg dose. In individual subjects, the mechanism-based inhibition model suggested that >90% inhibition of CYP2C8 was achieved with the 300-mg dose in 9 of the 10 subjects.

In the present study, only a small 0.25-mg dose of repaglinide, used as the CYP2C8 model substrate, was given for safety reasons. The relative roles of CYP2C8 and CYP3A4 may be slightly different with higher 0.5- to 4-mg doses of repaglinide (Bidstrup et al., 2003, 2006; Kajosaari et al., 2005a; Kalliokoski et al., 2008c). In any case, the consequences of CYP2C8 inhibition depend on the therapeutic index of the victim drug and the significance of CYP2C8 in its elimination. If other potential routes of elimination of CYP2C8 substrates are blocked by other drugs, or other routes are not functional, e.g., due to genetic factors, the inhibition of CYP2C8 enzyme may cause an unusually strong interaction.

To conclude, the interaction between gemfibrozil and repaglinide is dose dependent, with an incremental change in repaglinide plasma AUC and glucose-lowering effect and reduction in repaglinide metabolite formation with incremental single doses of 30, 100, 300, and 900 mg of gemfibrozil. The results are consistent with over 90 and 95% inhibition of hepatic CYP2C8 activity already with the 300- and 900-mg gemfibrozil doses. In clinical drug-interaction studies, a 300-mg gemfibrozil dose is sufficient to achieve similar inhibition of CYP2C8 as seen in in vivo probe. Drug Metab Dispos 37:2359–2366. Backman JT, Kyrklund C, Neuvonen M, and Neuvonen PJ (2002) Gemfibrozil greatly increases plasma concentrations of cerivastatin. Clin Pharmacol Ther 72:685–691.


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