BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2008.03287.x

The effect of *SLCO1B1* polymorphism on repaglinide pharmacokinetics persists over a wide dose range

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Keywords
OATP1B1, organic anion transporting polypeptide, pharmacogenetics, pharmacokinetics, repaglinide, *SLCO1B1*

Received
28 March 2008
Accepted
1 August 2008
Published *OnlineEarly*
24 September 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Organic anion transporting polypeptide 1B1 is an influx transporter expressed on the basolateral membrane of hepatocytes.
- A common single nucleotide polymorphism, c.521T→C (p.Val174Ala), of the *SLCO1B1* gene has been associated with increased plasma repaglinide concentrations in healthy volunteers.
- Previous studies at low repaglinide doses have suggested that the effect of *SLCO1B1* c.521T→C polymorphism on the pharmacokinetics of repaglinide could be dose-dependent.

WHAT THIS STUDY ADDS

- Repaglinide peak plasma concentration and area under the plasma concentration–time curve increased linearly along with repaglinide dose ranging from 0.25 to 2 mg in both the predominant c.521TT and rare c.521CC genotype group.
- The effect of *SLCO1B1* c.521T→C polymorphism on repaglinide pharmacokinetics persists over a wide dose range.

AIMS

To establish whether the effect of *SLCO1B1* [encoding organic anion transporting polypeptide 1B1 (OATP1B1)] c.521T→C (p.Val174Ala) polymorphism on the pharmacokinetics of repaglinide is dose-dependent.

METHODS

Twelve healthy volunteers with the *SLCO1B1* c.521TT genotype (controls) and eight with the c.521CC genotype ingested a single 0.25-, 0.5-, 1- or 2-mg dose of repaglinide in a dose-escalation study with a wash-out period of ≥1 week.

RESULTS

The mean area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$) of 0.25, 0.5, 1 or 2 mg repaglinide was 82% (95% confidence interval 47, 125), 72% (24, 138), 56% (24, 95) or 108% (59, 171) ($P \leq 0.001$) larger in participants with the *SLCO1B1* c.521CC genotype than in those with the c.521TT genotype, respectively. Repaglinide peak plasma concentration and $AUC_{0-\infty}$ increased linearly along with repaglinide dose in both genotype groups ($r > 0.88$, $P < 0.001$). There was a tendency towards lower blood glucose concentrations after repaglinide administration in the participants with the c.521CC genotype than in those with the c.521TT genotype.

CONCLUSIONS

The effect of *SLCO1B1* c.521T→C polymorphism on the pharmacokinetics of repaglinide persists throughout the clinically relevant dose range.

Introduction

Repaglinide, a short-acting insulin secretagogue, is used in reducing postprandial hyperglycaemia in patients with Type 2 diabetes mellitus [1]. Repaglinide has an oral bioavailability of about 60% [1, 2] and is biotransformed via the cytochrome P450 (CYP) 3A4 and 2C8 enzymes to several inactive metabolites, including M1, M2 and M4 [3–7]. Hepatic uptake by organic anion transporting polypeptide 1B1 (OATP1B1) is an important step preceding the metabolism of repaglinide in the liver [8, 9]. Repaglinide is available as 0.5-, 1- and 2-mg tablets, and the maximum daily dose is 16 mg [10].

Large interindividual variability, partly genetically determined, exists in the pharmacokinetics of repaglinide [1]. The *CYP2C8*3* allele has been associated with reduced plasma concentrations of repaglinide [11]. Moreover, subjects with the *SLCO1B1* (encoding OATP1B1) c.521CC genotype have had a 188% or 72% larger area under the plasma repaglinide concentration–time curve (AUC) than those with the c.521TT genotype after ingestion of 0.25 or 0.5 mg repaglinide, respectively [8, 12]. These findings suggest that the effect of *SLCO1B1* polymorphism on repaglinide pharmacokinetics could be less pronounced after higher repaglinide doses. One possible mechanism for these apparently dose-dependent findings is that the OATP1B1-mediated uptake of repaglinide is saturated already at low concentrations, and thus the effect of reduced OATP1B1 activity would be smaller at higher repaglinide doses. In this case, the effect of *SLCO1B1* polymorphism would be of limited importance at the doses used in clinical practice.

To establish whether the effect of the *SLCO1B1* c.521T→C (p.Val174Ala) single nucleotide polymorphism (SNP) on the pharmacokinetics of repaglinide is dose-dependent, we conducted a dose-escalation study in a panel of 20 healthy volunteers with different *SLCO1B1* genotypes. To exclude the effect of *CYP2C8*3* allele on the pharmacokinetics of repaglinide, only noncarriers of this allele were recruited.

Methods

Subjects

The study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District and by the National Agency for Medicines. All subjects gave their written informed consent. Participants were selected on the basis of the *SLCO1B1* c.521T→C SNP as well as the g.-11187G→A, g.-10499A→C and c.388A→G SNPs from a pool of genotyped healthy volunteers [13]. Haplotypes were assigned as described previously [13]. Only noncarriers of the *CYP2C8*3* allele were included [11]. The c.521TT (control) group comprised seven women and five men (mean ± SD age 24 ± 4 years, height 171 ± 8 cm, weight 71 ± 12 kg) with the homozygous reference genotype at each position (*SLCO1B1*1A/*1A*). The c.521CC group (age 24 ± 5 years, height 172 ± 7 cm, weight 70 ± 6 kg) included five women and three men. One of them had the *SLCO1B1*5/*17* genotype, three had the **15/*16* genotype and four had the **16/*17* genotype. Subjects were ascertained to be healthy by medical history, physical examination and laboratory tests before they were entered in the study. None was on any continuous medication and none was a tobacco smoker. Use of other drugs was prohibited for 1 week, use of grapefruit products for 3 days, and use of alcohol for 1 day before the day of repaglinide administration.

Study design

In a dose-escalation study with a wash-out period of ≥1 week, the subjects ingested, after an overnight fast, a single 0.25-, 0.5-, 1- or 2-mg dose of repaglinide (Novonorm; NovoNordisk, Bagsværd, Denmark) with 150 ml of water at 09.00 h. Repaglinide 0.25-mg tablets are not available and therefore repaglinide 0.5-mg tablets were halved and weighed by the investigators. Subjects remained seated for 3 h and received standardized meals: breakfast 15 min after administration of repaglinide, a snack after 1 and 2 h, a warm meal after 3 h, and a snack after 7 h. Additional carbohydrates were given if blood glucose concentration was low and/or the subject had symptoms of hypoglycaemia. Timed blood samples (5 or 10 ml each) were drawn prior to and 15, 30, 45, 60, 75, 90 and 105 min and 2, 2.5, 3, 4, 5 and 7 h after the administration of repaglinide. Blood glucose concentrations were measured immediately after each blood sampling by the glucose oxidase method with Precision G Blood Glucose Testing System (Medisense, Bedford, MA, USA). The between-day coefficient of variation (CV) of the method was 5.7% at 2.8 mmol l^{-1} and 4.4% at 18.6 mmol l^{-1} ($n = 28$). Plasma was separated within 30 min and stored at −70°C until analysis.

Determination of plasma drug concentrations

Plasma concentrations of repaglinide and its M1, M2 and M4 metabolites were quantified by use of an API 3000 liquid chromatography-tandem mass spectrometry (LC/MS/MS) system (Sciex Division of MDS Inc., Toronto, Ontario, Canada) as described previously [14]. The limit of quantification was 0.05 ng ml^{-1} for repaglinide, and the between-day CV was 9% at 0.1 ng ml^{-1} and 3% at 2.0 ng ml^{-1} and 20 ng ml^{-1} ($n = 21$). Because authentic metabolite standards were not available, plasma metabolite responses (relative concentrations) are given in arbitrary units relative to the ratio of the peak height of each metabolite to that of the internal standard, D5-repaglinide.

Pharmacokinetics and pharmacodynamics

The pharmacokinetics of repaglinide and its metabolites were characterized by the peak plasma concentration (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$) and

$AUC_{0-\infty}$. The elimination rate constant (k_e) was determined by linear regression analysis of the log-linear part of the concentration–time curve. The $t_{1/2}$ was calculated by the equation $t_{1/2} = \ln 2/k_e$. AUC was calculated by a combination of the linear (for increasing concentrations) and log-linear (for decreasing concentrations) trapezoidal rules, with extrapolation to infinity, when appropriate, by division of the last measured concentration by k_e. The blood glucose response to repaglinide was characterized by minimum blood glucose concentration, and the mean concentration from 0 to 3 h and from 0 to 7 h.

Statistical analysis

The data were analysed with the statistical program SPSS 13.0 (SPSS Inc., Chicago, IL, USA). C_{max} and AUC data were logarithmically transformed before statistical analysis. The pharmacokinetic (except t_{max}) and pharmacodynamic variables of repaglinide between the two *SLCO1B1* genotype groups were evaluated using repeated measures analysis of variance (ANOVA) including dose as a within-subjects factor and genotype as a between-subjects factor. Post hoc testing between the genotypes was done with independent samples *t*-test. The t_{max} data were compared between genotypes during each treatment phase with the Mann–Whitney *U*-test. The geometric mean ratio (c.521CC/c.521TT) with 95% confidence interval was calculated for repaglinide C_{max} and $AUC_{0-\infty}$ values. Dose linearity of repaglinide pharmacokinetics was investigated with linear regression analysis. A *P*-value <0.05 was considered to be statistically significant.

Results

Repaglinide pharmacokinetics

SLCO1B1 genotype was significantly associated with the pharmacokinetics of repaglinide after each dose (Table 1, Figure 1). The $AUC_{0-\infty}$ of repaglinide was 82, 72, 56 or 108% ($P \leq 0.001$) larger in participants with the c.521CC genotype than in those with the c.521TT genotype after ingestion of 0.25, 0.5, 1 or 2 mg repaglinide, respectively. The C_{max} of repaglinide was about 60–70% larger in the c.521CC participants than in the c.521TT participants ($P < 0.01$), except after the 1-mg dose with only a 32% larger ($P = 0.068$) C_{max}. No significant differences were seen in the t_{max} or $t_{1/2}$ of repaglinide between the genotype groups. The effect of *SLCO1B1* genotype on the pharmacokinetic variables of repaglinide was independent of repaglinide dose (Table 1). The increase of repaglinide C_{max} and $AUC_{0-\infty}$ was linear as a function of repaglinide dose in both genotype groups (Figure 2).

After each repaglinide dose, *SLCO1B1* genotype was significantly associated with the $AUC_{0-\infty}$ of repaglinide M2 and M4 metabolites, but not with that of M1, and the effect was independent of repaglinide dose (Table 1). There were no differences in the metabolite/repaglinide $AUC_{0-\infty}$ ratios between the two *SLCO1B1* genotype groups.

Repaglinide pharmacodynamics

There was a tendency towards lower blood glucose concentrations in the participants with the c.521CC genotype than in those with the c.521TT genotype during all phases (Figure 1), but no statistically significant differences were seen in repaglinide pharmacodynamic variables between the genotypes (Table 2). In addition to the standardized meals, four of the eight (50%) c.521CC participants and three of the 12 (25%) c.521TT participants received additional carbohydrates (14–123 g) after administration of 2 mg repaglinide to correct hypoglycaemia. After 1 mg repaglinide, additional carbohydrates were given to one c.521TT participant (14 g), and after 0.5 mg repaglinide to one c.521CC participant (63 g). Subjects reported only mild to moderate symptoms of hypoglycaemia, including reversible disturbance in attention, tremor, palpitations and headache.

Discussion

To our knowledge, this is the first study to investigate the effects of *SLCO1B1* polymorphism on drug pharmacokinetics at different doses. Repaglinide $AUC_{0-\infty}$ was 60–110% greater in participants with the c.521CC genotype than in those with the c.521TT genotype after ingestion of single repaglinide doses ranging from 0.25 to 2 mg. The effect of *SLCO1B1* genotype on repaglinide was independent of repaglinide dose, and the increase in repaglinide C_{max} and $AUC_{0-\infty}$ along with the dose was linear in both genotype groups. In agreement with the pharmacokinetic results, there was a tendency towards lower blood glucose concentrations after repaglinide administration in the participants with the c.521CC genotype than in those with the c.521TT genotype.

The *SLCO1B1* c.521T→C polymorphism is associated with increased C_{max} and AUC of repaglinide, with limited effects on its $t_{1/2}$, suggesting increased oral bioavailability or reduced clearance in association with a reduced distribution volume, or both. However, little has been known about the consistency of this effect at different doses. In a retrospective study, the mean AUC of 0.25 mg repaglinide was 188% larger in subjects with the c.521CC genotype than in those with the c.521TT genotype [8]. However, in two prospective studies with 0.25 or 0.5 mg of repaglinide, the mean AUC of repaglinide was only about 70% larger in the c.521CC group than in the c.521TT group [12, 15]. In any case, the results of the present study demonstrate that the effect of *SLCO1B1* polymorphism on repaglinide pharmacokinetics is independent of repaglinide dose. The apparent discrepancies in the previous studies could have been caused by random sampling variation, or by the low-

Table 1

Pharmacokinetic variables of repaglinide and its M1, M2 and M4 metabolites in healthy subjects with the *SLCO1B1* c.521TT ($n = 12$) or c.521CC ($n = 8$) genotype after a single oral 0.25-, 0.5-, 1- or 2-mg dose of repaglinide

Variable *SLCO1B1* genotype	Repaglinide 0.25 mg	Repaglinide 0.5 mg	Repaglinide 1 mg	Repaglinide 2 mg	ANOVA *P*-value for dose–group interaction
Repaglinide					
C_{max} (ng ml^{-1})					
c.521TT	3.7 ± 1.0	6.7 ± 2.4	16.5 ± 5.5	33.0 ± 8.5	0.485
c.521CC	6.2 ± 1.8**	11.5 ± 4.0**	21.6 ± 5.8	52.7 ± 11.7**	
Mean ratio (95% CI)†	1.65 (1.25, 2.19)	1.73 (1.19, 2.52)	1.32 (0.98, 1.79)	1.61 (1.26, 2.06)	
t_{max} (min)					
c.521TT	30 (30–60)	45 (30–120)	38 (30–45)	30 (30–45)	
c.521CC	30 (30–45)	30 (30–45)	30 (30–45)	45 (30–45)	
$t_{1/2}$ (h)					
c.521TT	1.5 ± 0.6	1.8 ± 0.5	1.7 ± 0.7	1.8 ± 0.6	0.680
c.521CC	1.7 ± 0.5	1.5 ± 0.3	1.7 ± 0.5	1.8 ± 0.4	
$AUC_{0-\infty}$ (ng ml^{-1} h^{-1})					
c.521TT	4.7 ± 1.1	10.3 ± 2.6	19.3 ± 4.2	37.2 ± 7.6	0.094
c.521CC	8.6 ± 1.8***	18.9 ± 9.6**	30.4 ± 7.8**	80.1 ± 27.4***	
Mean ratio (95% CI)†	1.82 (1.47, 2.25)	1.72 (1.24, 2.38)	1.56 (1.24, 1.95)	2.08 (1.59, 2.71)	
M1					
$AUC_{0-\infty}$ (U ml^{-1} h^{-1})					
c.521TT	15.6 ± 14.1	35.8 ± 34.8	58.8 ± 38.1	106.5 ± 91.3	0.838
c.521CC	14.0 ± 6.2	27.7 ± 11.5	54.2 ± 27.2	96.5 ± 41.3	
M1/Repaglinide $AUC_{0-\infty}$ ratio (U ng^{-1})					
c.521TT	3.6 ± 3.8	3.9 ± 4.8	3.4 ± 2.9	3.0 ± 2.9	0.771
c.521CC	1.7 ± 0.9	1.7 ± 0.9	1.8 ± 0.7	1.3 ± 0.7	
M2					
$AUC_{0-\infty}$ (U ml^{-1} h^{-1})					
c.521TT	20.9 ± 13.9	45.3 ± 34.2	93.2 ± 60.1	137.8 ± 95.7	0.883
c.521CC	49.7 ± 34.4**	92.9 ± 57.1*	193.0 ± 154.2*	295.3 ± 162.6*	
M2/Repaglinide $AUC_{0-\infty}$ ratio (U ng^{-1})					
c.521TT	4.6 ± 3.7	4.8 ± 5.0	5.3 ± 4.5	3.8 ± 3.1	0.384
c.521CC	6.0 ± 4.4	5.8 ± 3.8	6.0 ± 3.3	3.8 ± 2.0	
M4					
$AUC_{0-\infty}$ (U ml^{-1} h^{-1})					
c.521TT	24.4 ± 19.8	47.1 ± 30.8	91.9 ± 60.2	169.6 ± 141.3	0.567
c.521CC	39.2 ± 15.6*	83.0 ± 41.2*	160.9 ± 103.4*	308.3 ± 117.3**	
M4/Repaglinide $AUC_{0-\infty}$ ratio (U ng^{-1})					
c.521TT	5.5 ± 5.4	4.9 ± 4.3	5.4 ± 5.1	4.8 ± 4.7	0.229
c.521CC	4.7 ± 2.0	5.0 ± 2.7	5.1 ± 2.1	4.0 ± 1.3	

Data are mean ± SD, t_{max} data are median (range). C_{max}, peak plasma concentration; CI, confidence interval; t_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 h to infinity. *$P < 0.05$ *vs.* c.521TT group; **$P < 0.01$ *vs.* c.521TT group; ***$P < 0.001$ *vs.* c.521TT group. †These data are geometric mean ratio (95% CI) c.521CC *vs.* c.521TT group.

activity *SLCO1B1*1B* (c.388G-c.521T) allele [16, 17], the carriers of which were not excluded from the retrospective study [8].

The difference in the AUC of repaglinide between the two *SLCO1B1* genotype groups was larger, although not statistically significantly, after ingesting 2 mg repaglinide than after the lower repaglinide doses. Therefore, the possibility that the effect of *SLCO1B1* genotype on repaglinide pharmacokinetics could increase after administering ≥2 mg repaglinide cannot be excluded. In this study, higher repaglinide doses were not administered due to the risk of profound hypoglycaemia in healthy volunteers.

The present study has confirmed the relevance of the *SLCO1B1* c.521T→C polymorphism to the pharmacokinetics of repaglinide over the dose range used in clinical practice. Moreover, the pharmacokinetics of repaglinide proved to be linear in both the predominant c.521TT and the rare c.521CC (about 2–5% of Whites and 1–2% of Asians) [13, 18–21] genotype group, similar to what has been seen in subjects not genotyped for *SLCO1B1* polymorphism [1].

It should be recognized that the pharmacodynamics of repaglinide cannot be directly extrapolated from healthy subjects to patients with Type 2 diabetes mellitus. The pharmacokinetics of repaglinide, however, is similar in both healthy subjects and patients, and repaglinide exhibits a clear dose–response [1]. Therefore, patients homozygous for the *SLCO1B1* c.521C allele are probably more susceptible to the blood glucose-lowering effect of repaglinide than those with other genotypes. Based on the pharmacokinetic results of the present study, the optimal

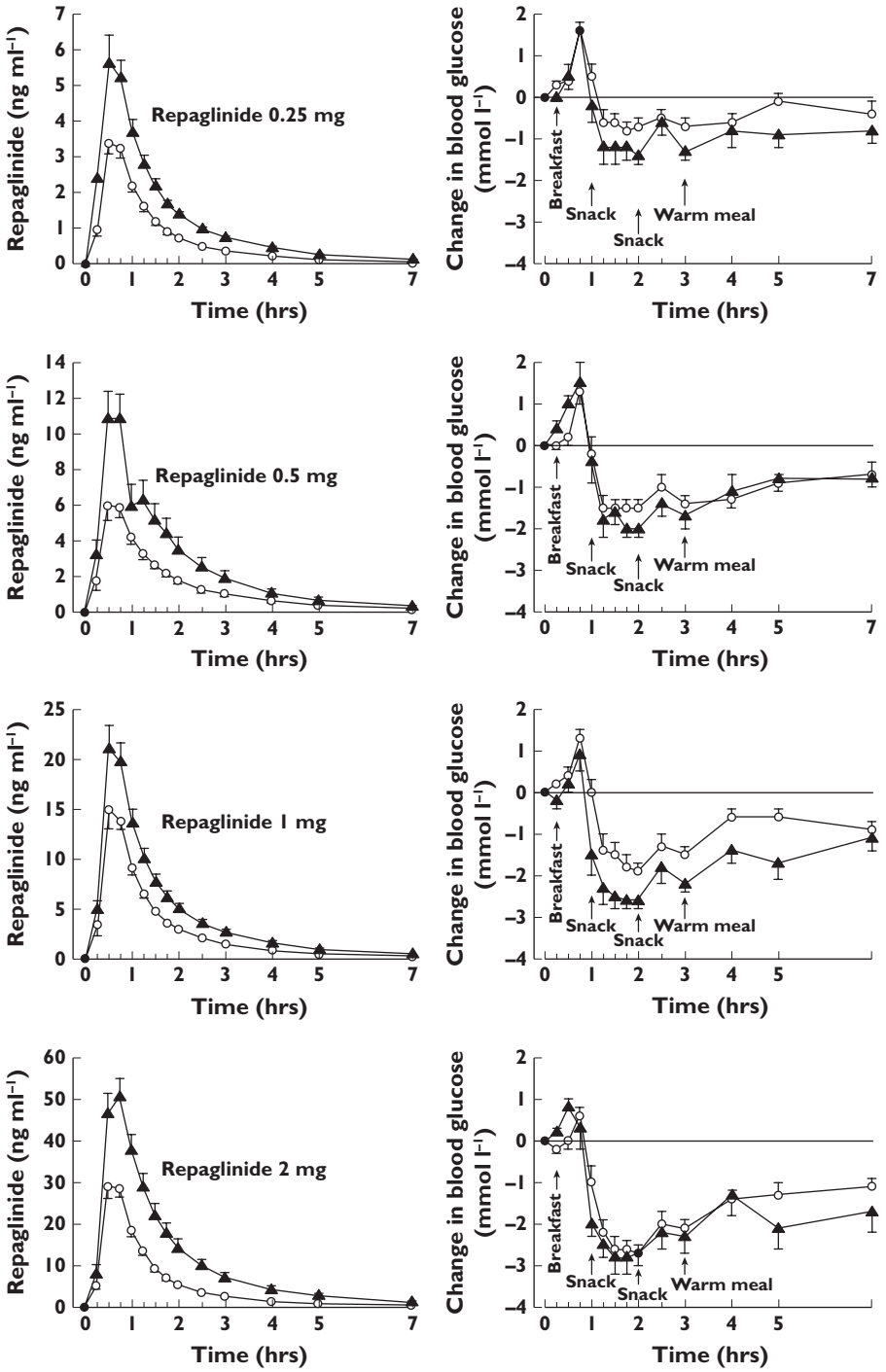

Figure 1

Mean ± SEM plasma concentrations of repaglinide and change in blood glucose concentrations after a single 0.25, 0.5, 1 or 2 mg oral dose of repaglinide in healthy subjects with the *SLCO1B1* c.521TT ($n = 12$, open circles) or c.521CC ($n = 8$, solid triangles) genotype. Due to hypoglycaemia, additional carbohydrates were given after 2 mg repaglinide to four c.521CC participants and three c.521TT participants (14–123 g), after 1 mg repaglinide to one c.521TT participant (14 g), and after 0.5 mg repaglinide to one c.521CC participant (63 g). Some error bars have been omitted for clarity. c.521TT (○); c.521CC (▲)

starting dose of repaglinide could be about 50% lower in patients with the c.521CC genotype than in those with the c.521TT genotype. Obviously, the dose of repaglinide should be adjusted according to the actual blood glucose-lowering response. Selecting the starting dose according to genotype might reduce the time needed to reach the correct maintenance dose, potentially with a smaller risk of hypoglycaemia.

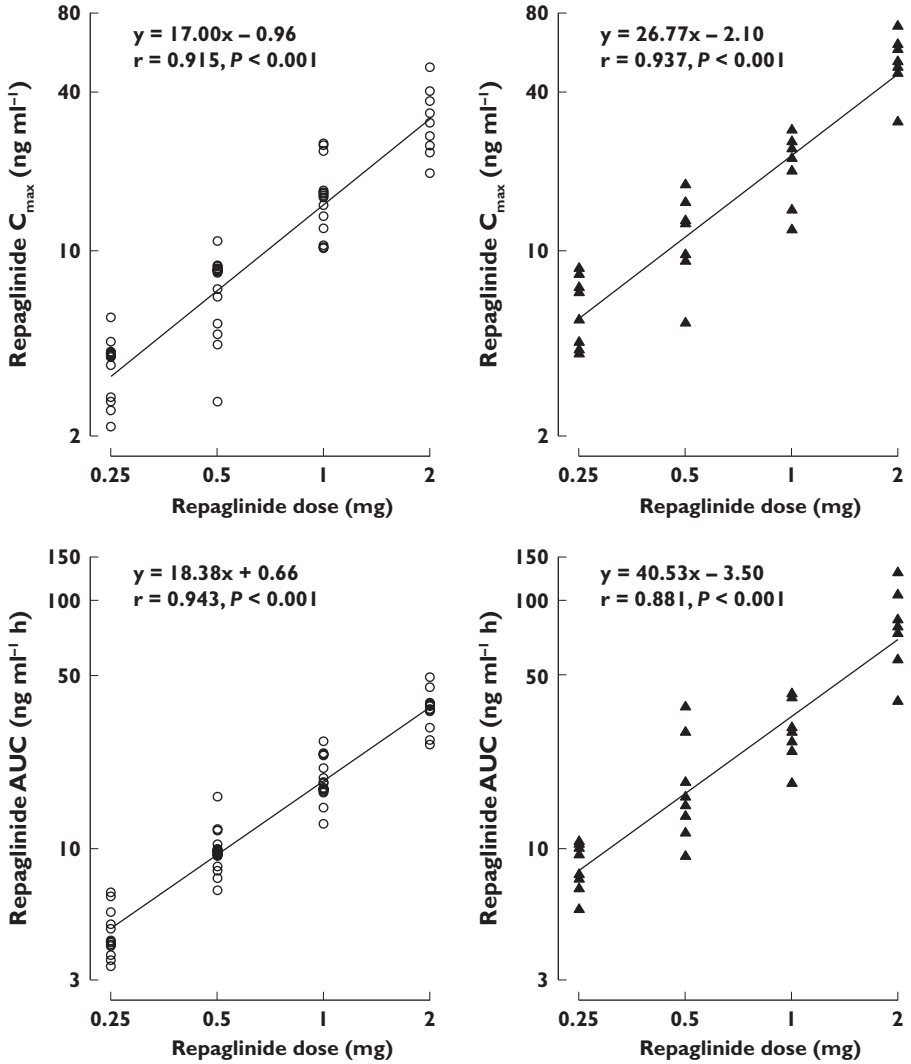

Figure 2

The individual repaglinide C_{max} and $AUC_{0-\infty}$ values after a single 0.25-, 0.5-, 1- or 2-mg oral dose of repaglinide in healthy subjects with the *SLCO1B1* c.521TT ($n = 12$, open circles) or c.521CC ($n = 8$, solid triangles) genotype. c.521TT (○); c.521CC (▲)

Table 2

Blood glucose variables of a single oral 0.25-, 0.5-, 1- or 2-mg dose of repaglinide in healthy subjects with the *SLCO1B1* c.521TT ($n = 12$) or c.521CC ($n = 8$) genotype

Variable *SLCO1B1* genotype	Repaglinide 0.25 mg	Repaglinide 0.5 mg	Repaglinide 1 mg	Repaglinide 2 mg	ANOVA *P*-value for dose–group interaction
Minimum concentration (mmol l^{-1})					
c.521TT	3.7 ± 0.6	3.2 ± 0.5	2.9 ± 0.8	2.3 ± 0.5	0.539
c.521CC	3.4 ± 0.6	3.1 ± 0.7	2.5 ± 0.6	2.1 ± 0.5	
Mean concentration (mmol l^{-1}) 0–3 h					
c.521TT	4.9 ± 0.6	4.7 ± 0.6	4.3 ± 0.7	3.8 ± 0.5	0.610
c.521CC	4.9 ± 0.4	4.6 ± 0.7	4.1 ± 0.5	3.6 ± 0.3	
Mean concentration (mmol l^{-1}) 0–7 h					
c.521TT	4.8 ± 0.4	4.5 ± 0.5	4.3 ± 0.5	3.9 ± 0.5	0.126
c.521CC	4.7 ± 0.5	4.5 ± 0.7	4.0 ± 0.6	3.5 ± 0.6	

Data are mean ± SD.

In addition to repaglinide, the *SLCO1B1* c.521T→C polymorphism has been associated with the pharmacokinetics of several other drugs, such as fexofenadine, pravastatin, simvastatin, atorvastatin and rosuvastatin [22–27], but different doses have not been addressed in these studies. For example, statins generally have a large dose range of up to eightfold [28], and data on the effect of the *SLCO1B1* genotype in relation to dose could be useful in adjusting statin dosage. Such information might also be valuable in tailoring treatment of drugs with a narrow therapeutic range, such as SN-38, the active metabolite of the antineoplastic agent irinotecan, the concentrations of which have been higher in patients carrying the *SLCO1B1* c.521C allele than in noncarriers [29].

In conclusion, the effect of *SLCO1B1* c.521T→C polymorphism on the pharmacokinetics of repaglinide persists throughout the clinically relevant dose range. Further studies are warranted to establish the relevance of *SLCO1B1* polymorphism on the blood glucose-lowering effect of repaglinide in patients with Type 2 diabetes mellitus.

The authors thank Ms Kerttu Mårtensson, Ms Eija Mäkinen-Pulli, Ms Lisbet Partanen, Ms Anna-Riitta Pasanen and Mr Jouko Laitila for skilful assistance, and Mr Harri Paakkulainen for statistical advice. This study was supported by grants from the Helsinki University Central Hospital Research Fund (Helsinki, Finland) and the Sigrid Jusélius Foundation (Helsinki).

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