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Effect of *ABCB1* polymorphisms and atorvastatin on sitagliptin pharmacokinetics in healthy volunteers

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Abstract

Objectives—The objectives of this study were to determine if *ABCB1* polymorphisms are associated with interindividual variability in sitagliptin pharmacokinetics, and if atorvastatin alters the pharmacokinetic disposition of sitagliptin in healthy volunteers.

Methods—In this open-label, randomized, two-phase crossover study, healthy volunteers were prospectively stratified according to *ABCB1* 1236/2677/3435 diplotype (n=9, CGC/CGC; n=10, CGC/TTT; and n=10, TTT/TTT). In one phase, participants received a single 100 mg dose of sitagliptin. In the other phase, participants received 40 mg of atorvastatin for five days, with a single 100 mg dose of sitagliptin administered on day 5. A 24 hour pharmacokinetic study followed each sitagliptin dose, and the study phases were separated by a 14-day washout period.

Results—Sitagliptin pharmacokinetic parameters did not differ significantly between *ABCB1* CGC/CGC, CGC/TTT, and TTT/TTT diplotype groups during the monotherapy phase. Atorvastatin administration did not significantly affect sitagliptin pharmacokinetics, with GMRs (90% CIs) for sitagliptin C_{max} , $AUC_{0-\infty}$, CL_R , and f_e of 0.93 (0.86, 1.01), 0.96 (0.91, 1.01), 1.02 (0.93, 1.12), and 0.98 (0.90, 1.06), respectively.

Conclusions—*ABCB1* CGC/CGC, CGC/TTT, and TTT/TTT diplotypes did not influence sitagliptin pharmacokinetics in healthy volunteers. Furthermore, atorvastatin had no effect on the pharmacokinetics of sitagliptin in the setting of *ABCB1* CGC/CGC, CGC/TTT, and TTT/TTT diplotypes.

Keywords

sitagliptin; atorvastatin; *ABCB1*; P-glycoprotein; pharmacogenetic; pharmacokinetic

Introduction

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that is used in the treatment of type 2 diabetes [1-3]. Sitagliptin undergoes little hepatic metabolism, and about 80% of the drug is excreted unchanged in the urine, mainly through active tubular secretion [2,4,5]. In vitro and clinical data suggest that sitagliptin is a substrate for the efflux transporter, P-glycoprotein (P-gp) [6,7]. P-gp is expressed on the brush border membrane of intestinal

enterocytes and the luminal side of renal proximal tubular cells [8]. It can be hypothesized that interindividual variability in P-gp-mediated transport of sitagliptin, as a result of genetic polymorphisms or drug-drug interactions, may contribute to alterations in sitagliptin pharmacokinetics in humans.

The most commonly studied polymorphisms in *ABCB1*, the gene that encodes P-gp, are c.1236C>T (rs1128503), c.2677G>T/A (rs2032582), and c.3435C>T (rs1045642), and these polymorphisms are often evaluated in haplotype form (i.e., 1236/2677/3435) [9]. In vitro, *ABCB1* 3435T, in combination with 1236T and/or 2677T, has been associated with changes in P-gp conformation and decreased P-gp function [10]. *ABCB1* 3435T has also been shown to affect mRNA stability [11]. In vivo, there are conflicting reports regarding the association between *ABCB1* genetics and drug exposure for different P-gp substrates [9,12]. To our knowledge, the extent to which common *ABCB1* SNPs affect sitagliptin pharmacokinetics has not been studied.

Atorvastatin, an HMG-CoA reductase inhibitor (statin), is used to lower cholesterol and reduce the risk of cardiovascular disease in patients with type 2 diabetes [13-19]. In vitro data show that atorvastatin is both a substrate and an inhibitor of P-gp [20-27]. In clinical studies, atorvastatin has been shown to alter the pharmacokinetics of the P-gp substrates, digoxin and aliskiren [21,28]. Sitagliptin and atorvastatin are frequently co-administered in patients with type 2 diabetes; however, a pharmacokinetic assessment of the effect of atorvastatin on sitagliptin disposition has not been conducted in humans.

Given the gaps in knowledge regarding the impact of *ABCB1* genetics and P-gp-mediated drug-drug interactions on sitagliptin disposition, the objectives of our study were to: 1) determine if *ABCB1* polymorphisms are associated with interindividual variability in sitagliptin pharmacokinetics, and 2) determine if atorvastatin alters sitagliptin pharmacokinetics in healthy volunteers.

Materials and methods

Study design

The investigation was conducted as an open-label, randomized, two-phase crossover study in healthy volunteers prospectively stratified according to *ABCB1* diplotype. In one phase, participants received a single 100 mg dose of sitagliptin by mouth at 8:00 AM. In the other phase, participants received 40 mg of atorvastatin by mouth at 8:00 AM for five days, with a single 100 mg dose of sitagliptin administered by mouth at 8:00 AM on day 5. A 14-day washout period separated the two phases. After each sitagliptin dose, an intensive 24-hour pharmacokinetic study was conducted at the University of Colorado Clinical and Translational Research Center (CTRC). Participants started the pharmacokinetic studies in the fasted state and a standardized breakfast (600 calories; 55% carbohydrates, 15% protein, and 30% fat) was administered two hours after sitagliptin dosing. Warm meals were also given 6, 10, and 24 hours after sitagliptin administration. Participants abstained from caffeine and smoking during the 24-hour period. Blood samples (5 ml in EDTA) were collected pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours post-dosing in both phases. Plasma was harvested within 30 minutes and stored at -80°C until analytical processing. Urine, which was kept on ice, was collected from 0 to 12 hours and 12 to 24 hours. The volume of urine collected during each 12-hour period was recorded. A 10 ml urine aliquot was removed and stored at -80°C until analytical processing. Blood glucose was measured by finger-stick at 1, 2, 3, and 4 hours after sitagliptin administration to assess for hypoglycemia.

Study participants

Healthy men and women between 21 to 60 years of age were recruited to participate in the study, which was approved by the Colorado Multiple Institutional Review Board. All subjects provided written informed consent. Participants were prospectively screened and stratified according to *ABCB1* (1236/2677/3435) diplotype as follows: Group 1, CGC/CGC (reference); Group 2, CGC/TTT; and Group 3, TTT/TTT.

For inclusion in the study, metabolic, renal, hepatic, and hematologic laboratory parameters had to be within normal limits. Participants were excluded for any of the following: current or past history of cardiovascular, hepatic, renal, endocrine, gastrointestinal, pulmonary, hematologic, immunologic, or neurologic diseases. Other pertinent exclusion criteria were: body mass index (BMI) $<18 \text{ kg/m}^2$ or $>30 \text{ kg/m}^2$; body weight $<50 \text{ kg}$; creatinine clearance $<60 \text{ ml/min}$ based on the Cockcroft-Gault formula; lipid-lowering therapy (e.g., statins); inhibitors or inducers of P-gp or CYP3A4; and/or medications known to affect drug absorption (e.g., cholestyramine).

Genetic analyses

For the screening genetic sample, a buccal cell sample was collected via a mouthwash method [29]. Genomic DNA was isolated using a QIAamp DNA Mini Kit (Qiagen, Valencia, CA, USA). The *ABCB1* polymorphisms, c.1236C>T (rs1128503), c.2677G>T/A (rs2032582), and c.3435C>T (rs1045642), were genotyped by PCR-pyrosequencing (PSQ 96MA, Qiagen, Valencia, CA, USA). *ABCB1* haplotypes and diplotypes were computationally assigned using HelixTree Genetics Analysis Software (Golden Helix, Bozeman, MT, USA).

Drug concentration analyses

Plasma and urine concentrations of sitagliptin and plasma concentrations of atorvastatin and its metabolites (i.e., atorvastatin lactone, 4-hydroxyatorvastatin, 4-hydroxyatorvastatin lactone, 2-hydroxyatorvastatin, and 2-hydroxyatorvastatin lactone) were measured with a validated LC/MS-MS assay. The detailed bioanalytical methods are provided in the supplementary appendix. The limits of quantification (LOQs) for sitagliptin in plasma and in urine were 0.22 ng/ml and 0.11 ng/ml, respectively. The LOQs for atorvastatin and its metabolites in plasma were: atorvastatin, 0.60 ng/ml; atorvastatin lactone, 0.31 ng/ml; 4-hydroxyatorvastatin, 0.30 ng/ml; 4-hydroxyatorvastatin lactone, 0.29 ng/ml; 2-hydroxyatorvastatin, 0.60 ng/ml; and 2-hydroxyatorvastatin lactone, 0.62 ng/ml. The between-day coefficient of variation (CV) for plasma sitagliptin was 12% for low concentration quality controls, and less than 10% for medium and high concentration quality controls. For plasma atorvastatin and its metabolites, the between-day CVs for low concentration quality controls were 13% (atorvastatin) and less than 20% (atorvastatin metabolites). The CVs for medium and high concentration quality controls were less than 16% for atorvastatin and its metabolites.

Pharmacokinetic analyses

Plasma concentration-time curves of sitagliptin, atorvastatin (acid), atorvastatin lactone, and atorvastatin metabolites were generated and the maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were taken from the curves. Pharmacokinetic parameters were estimated using noncompartmental methods with WinNonlin version 5.2.1 software (Pharsight Corporation, Mountain View, CA, USA). The terminal elimination rate constant (λ_z) was obtained by regression of the log-linear portion of the concentration-time curves. Sitagliptin area under the plasma concentration-time curve from 0 to infinity ($\text{AUC}_{0-\infty}$) and 0 to 24 hours (AUC_{0-24}), and atorvastatin acid, atorvastatin lactone, and atorvastatin

metabolites AUC over the dosing interval (AUC_{τ}) were calculated using the linear-log trapezoidal rule. Half-lives ($t_{1/2}$) were calculated as 0.693 divided by λ_z . For the calculation of sitagliptin renal clearance (CL_R), the amount of sitagliptin collected over each 12-hour period was multiplied by the urine volume collected during that period and the two amounts were summed. The fraction of sitagliptin excreted unchanged in the urine (f_e) was calculated as the total amount of sitagliptin excreted during the 24-hour period divided by dose. CL_R was determined as the product of f_e and CL/F .

Statistical analyses

Baseline demographics were compared between *ABCB1* 1236/2677/3435 diplotype groups using Fisher exact tests for categorical variables and one-way analysis of variance for continuous variables. Pharmacokinetic parameters that did not follow a normal distribution were log-transformed for statistical analysis and then back-transformed for data presentation. For the assessment of the potential interaction between sitagliptin and atorvastatin, sitagliptin pharmacokinetic parameters were presented as 90% confidence intervals (CI) surrounding the geometric mean ratios (GMR). The 90% CIs were compared to the pre-specified no effect bounds of 0.8-1.25. If the 90% CI of sitagliptin $AUC_{0-\infty}$ fell entirely within the pre-specified bounds, it was concluded that atorvastatin did not have a clinically significant effect on sitagliptin exposure [30]. Pharmacokinetic data were compared within each *ABCB1* diplotype group using paired *t* tests or Wilcoxon signed rank tests (for time data). Pharmacokinetic data, including relative changes, were compared between *ABCB1* diplotype groups using one-way analysis of variance, Kruskal-Wallis tests (for time data), or generalized linear model analysis (for assessment of covariates). An *a priori* power calculation is provided in the supplementary appendix. Statistical analyses were conducted using SPSS version 18.0 software. A *P* value <0.05 was considered statistically significant.

Results

We prospectively screened 145 subjects for *ABCB1* 1236/2677/3435 diplotypes, and 33 subjects started the study protocol. Four subjects participated in only one phase of the study—two withdrew for personal reasons and two were withdrawn for adverse events (i.e., increased liver function tests and difficulty maintaining intravenous access). Here, we present the results of 29 subjects who completed both phases of the study. The study consisted of 16 men and 13 women, mean age 33 ± 10 years, mean weight 73.0 ± 9.9 kg, and mean creatinine clearance 100.0 ± 14.5 ml/min. Table 1 shows baseline demographics by *ABCB1* diplotype group [CGC/CGC (n=9), CGC/TTT (n=10), and TTT/TTT (n=10)]. With the exception of race ($p=0.05$), baseline variables did not differ significantly among the three diplotype groups.

During the sitagliptin monotherapy phase, there was modest variability in sitagliptin C_{\max} , $AUC_{0-\infty}$, and AUC_{0-24} , with CV% of 37%, 33%, and 32%, respectively. In terms of *ABCB1* genetics, the pharmacokinetics of sitagliptin (when administered alone) did not differ significantly between CGC/CGC, CGC/TTT, and TTT/TTT diplotype groups (Table 2). Sitagliptin CL_R and f_e were numerically greater in the TTT/TTT group as compared with the CGC/TTT and CGC/CGC groups; however these results did not reach statistical significance ($p=0.21$ and $p=0.44$, respectively), even when controlling for creatinine clearance ($p=0.36$ and $p=0.64$, respectively).

Atorvastatin administration did not significantly affect sitagliptin pharmacokinetics (Figure 1 and Table 3), with 90% CIs that fell within the pre-specified bounds of 0.8 to 1.25. Median sitagliptin T_{\max} was 3 hours in the absence and presence of atorvastatin. *ABCB1* diplotype did not influence sitagliptin pharmacokinetics in the presence of atorvastatin (Table 2).

Likewise, mean relative changes in sitagliptin pharmacokinetic parameters did not differ significantly within or between *ABCB1* diplotype groups (Table 2). When the analysis was restricted to Caucasians only, there were no significant differences in sitagliptin pharmacokinetic parameters between *ABCB1* diplotype groups in the monotherapy phase, in the presence of atorvastatin, or for relative changes (data not shown).

Atorvastatin and atorvastatin lactone pharmacokinetic parameters did not differ significantly between *ABCB1* diplotype groups (Table 4). Along the same lines, the pharmacokinetics of 2-hydroxyatorvastatin, 2-hydroxyatorvastatin lactone, 4-hydroxyatorvastatin, and 4-hydroxyatorvastatin lactone were not significantly affected by *ABCB1* diplotype (Table 4).

Discussion

We sought to determine the impact of *ABCB1* polymorphisms and atorvastatin on sitagliptin pharmacokinetics in healthy volunteers. Our main finding was that sitagliptin pharmacokinetics did not differ between *ABCB1* diplotypes (i.e., CGC/CGC, CGC/TTT, and TTT/TTT). We also found that atorvastatin did not alter the disposition of sitagliptin.

Given in vitro data showing that *ABCB1* polymorphisms have putative functional consequences [10,11,31,32], we hypothesized that the *ABCB1* 1236T/2677T/3435T haplotype may be associated with increased sitagliptin plasma exposure as a result of decreased renal clearance and/or increased oral bioavailability of sitagliptin. Our findings do not support this hypothesis, as sitagliptin plasma exposure did not differ significantly between *ABCB1* CGC/CGC, CGC/TTT, and TTT/TTT diplotype groups. This does not imply that P-gp does not have a role in sitagliptin disposition, but rather, that *ABCB1* CGC/CGC, CGC/TTT, and TTT/TTT diplotypes do not significantly influence sitagliptin pharmacokinetics in vivo. Similar findings have been observed for the P-gp substrate, digoxin, whereby *ABCB1* polymorphisms have been shown to have no impact on digoxin pharmacokinetics in some clinical studies [31,33]. It is well-known that *ABCB1* pharmacogenetic studies are influenced by confounding factors (e.g., race, co-medication, genotype versus haplotype); therefore the influence of *ABCB1* genetics on the disposition of sitagliptin merits study in additional cohorts [31]. In vitro data also indicate that sitagliptin is a substrate for other drug transporters such as human organic anion transporter 3 (hOAT3) and organic anion transporting polypeptide 4C1 (OATP4C1) [6]. As such, the effect of OAT3 and OATP4C1 gene polymorphisms on sitagliptin disposition warrants investigation in clinical studies.

Sitagliptin is commonly co-administered with atorvastatin in clinical practice [19]. Atorvastatin has been shown to significantly increase the plasma concentrations of P-gp substrates such as digoxin, aliskiren, and verapamil, in healthy volunteers [21,28,34]. We found that sitagliptin pharmacokinetic parameters were unchanged following steady-state administration of atorvastatin. These results are consistent with the fact that atorvastatin is not a potent inhibitor of P-gp in vivo, producing plasma concentrations that are often much lower than its IC₅₀ [35,7]. In terms of other, more potent, P-gp inhibitors, a healthy volunteer study showed a single 600 mg dose of cyclosporine modestly increased sitagliptin C_{max}, but did not have a significant effect on overall sitagliptin plasma exposure [7]. Taken together, it does not appear that inhibition of P-gp alters sitagliptin disposition to a great extent in humans. Our drug interaction assessment was conducted in the setting of a diplotype enrichment design; therefore the findings are only applicable to individuals with *ABCB1* CGC/CGC, CGC/TTT, or TTT/TTT diplotypes. We also studied a moderate, 40 mg dose of atorvastatin. It remains to be determined whether atorvastatin administration in the setting of other *ABCB1* diplotypes, or high-dose atorvastatin (80 mg), has a clinically meaningful impact on sitagliptin concentrations. This is unlikely given the low frequency

and questionable functional significance of other polymorphic *ABCB1* diplotypes, the absence of any interaction with the 40 mg dose, and the wide therapeutic index of sitagliptin [2,36,37,7].

Our drug interaction findings are consistent with data showing that statins do not alter the concentrations of other DPP-4 inhibitors (e.g., alogliptin, vildagliptin, saxagliptin) to an appreciable extent [38]. For example, atorvastatin 80 mg and simvastatin 80 mg did not alter the multiple-dose pharmacokinetics of alogliptin and vildagliptin, respectively, in healthy volunteers [39,40]. Simvastatin 40 mg increased saxagliptin C_{max} by 21% and AUC by 12%; however the magnitude of this interaction was determined not to be clinically significant [41]. We did not assess the impact of sitagliptin on atorvastatin pharmacokinetics because evidence suggests that sitagliptin does not inhibit or induce CYP3A4 or P-gp [3]. However, a few patient case reports have been published, which attribute the development of rhabdomyolysis to the concomitant administration of sitagliptin with various statins (e.g., lovastatin, simvastatin, and atorvastatin) [42-44]. Healthy volunteer studies do not indicate that DPP-4 inhibitors have a major effect on statin pharmacokinetics; therefore, the mechanisms underlying the observations in these case reports are unclear [38].

We found no differences in atorvastatin or atorvastatin metabolite disposition between CGC/CGC, CGC/TTT, and TTT/TTT diplotypes [45]. In contrast, a few studies have shown that *ABCB1* haplotypes influence atorvastatin pharmacokinetics in healthy volunteers. Keskitalo et al. found that atorvastatin acid, 2-hydroxyatorvastatin, and 4-hydroxyatorvastatin plasma exposures were greater in Caucasian subjects with the TTT/TTT diplotype than in those with the CGC/CGC diplotype [45]. Lee et al. found that atorvastatin, atorvastatin lactone, 2-hydroxyatorvastatin, and 2-hydroxyatorvastatin lactone half-lives, but not plasma exposures, were greater in Korean subjects with two copies of the 267TT/3435T haplotype as compared with the GC/GC and GC/TT diplotypes [46]. Unlike these previous studies, we did not interrogate *SLCO1B1* hepatic uptake transporter polymorphisms, which are known to influence statin pharmacokinetics [47]. Therefore, *SLCO1B1* polymorphisms may have confounded our assessment of the influence of *ABCB1* polymorphisms on atorvastatin disposition. Other possible reasons for the discrepancies between studies may include: different race/ethnic demographics of the study cohorts, small sample size, concomitant medications (e.g., sitagliptin), and failure to consider polymorphisms in other drug metabolizing enzyme and transporter genes (e.g., *CYP3A5*, *ABCG2*).

In conclusion, sitagliptin pharmacokinetics did not differ between *ABCB1* CGC/CGC, CGC/TTT, and TTT/TTT diplotypes in healthy volunteers. Furthermore, atorvastatin had no effect on the pharmacokinetics of sitagliptin in the setting of this *ABCB1* diplotype enrichment study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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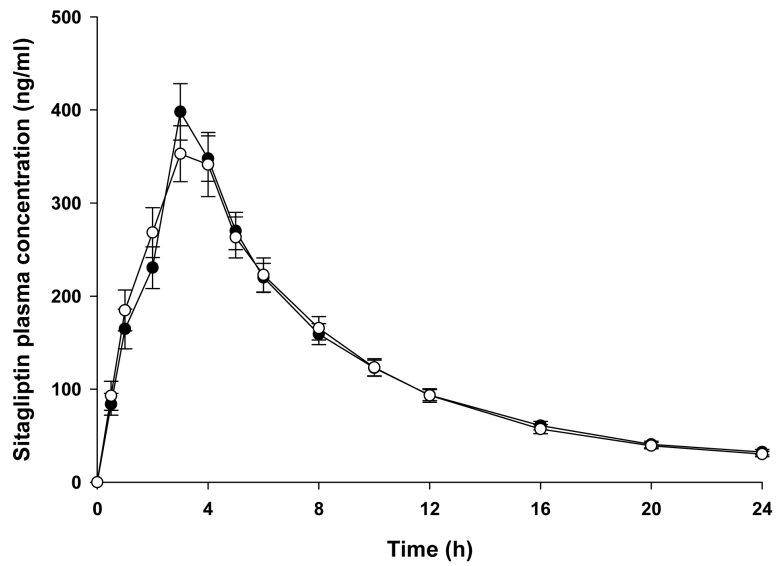


Fig.1. Sitagliptin plasma concentrations (mean \pm standard error) in the absence (*closed circles*) and presence (*open circles*) of atorvastatin in all study participants (n=29).

Table 1Baseline demographics (n=29) by *ABCB1* 1236/2677/3435 diplotype group

Variable	<i>ABCB1</i> CGC/CGC n=9	<i>ABCB1</i> CGC/TTT n=10	<i>ABCB1</i> TTT/TTT n=10	<i>P</i> value
Male, n	4	8	4	0.17
Race, n				
Caucasian	5	6	10	0.05
African American	3	1	0	
Other	1	3	0	
Age, years	36 ± 10	33 ± 10	32 ± 10	0.71
Weight, kg	75.9 ± 10.5	68.7 ± 7.5	74.8 ± 10.9	0.23
Creatinine Clearance, ml/min	99.2 ± 12.9	95.8 ± 15.7	104.9 ± 14.7	0.38
Current smoker	2	2	0	0.42
Hormonal birth control	2	1	1	0.66

Data are expressed as number or mean ± standard deviation. Creatinine clearance was calculated by the Cockcroft-Gault equation.

Table 2

Single-dose sitagliptin pharmacokinetics in the presence and absence of atorvastatin by *ABCB1* diplotype group

Pharmacokinetic parameter	Sitagliptin Alone Arithmetic Mean \pm SD	Sitagliptin + Atorvastatin Arithmetic Mean \pm SD	Mean relative change (95% CI)	P Value (within diplotype groups)
<i>C</i> _{max} (ng/ml)				
<i>ABCB1</i> CGC/CGC	454 \pm 180	428 \pm 201	0.96 (0.75-1.17)	0.43
<i>ABCB1</i> CGC/TTT	438 \pm 152	420 \pm 137	1.0 (0.79-1.21)	0.69
<i>ABCB1</i> TTT/TTT	394 \pm 160	370 \pm 217	0.93 (0.76-1.11)	0.26
P value, between diplotype groups	0.67	0.56	0.86	
AUC _{0-∞} (ng*h/ml)				
<i>ABCB1</i> CGC/CGC	3638 \pm 1439	3501 \pm 1617	0.96 (0.81-1.11)	0.41
<i>ABCB1</i> CGC/TTT	3502 \pm 1133	3430 \pm 1279	0.98 (0.88-1.07)	0.43
<i>ABCB1</i> TTT/TTT	3129 \pm 795	3117 \pm 1216	0.97 (0.87-1.08)	0.45
P value, between diplotype groups	0.83	0.90	0.97	
AUC ₀₋₂₄ (ng*h/ml)				
<i>ABCB1</i> CGC/CGC	3227 \pm 1216	3205 \pm 1420	0.99 (0.83-1.15)	0.66
<i>ABCB1</i> CGC/TTT	3081 \pm 925	3073 \pm 1101	0.99 (0.89-1.09)	0.69
<i>ABCB1</i> TTT/TTT	2809 \pm 820	2799 \pm 1195	0.98 (0.92-1.04)	0.42
P value, between diplotype groups	0.80	0.82	0.97	
CL _R ^a (ml/min)				
<i>ABCB1</i> CGC/CGC	254 \pm 176	280 \pm 124	1.22 (0.97-1.48)	0.11
<i>ABCB1</i> CGC/TTT	232 \pm 62	226 \pm 66	0.99 (0.82-1.16)	0.67
<i>ABCB1</i> TTT/TTT	359 \pm 182	339 \pm 188	1.0 (0.81-1.18)	0.68
P value, between diplotype groups	0.21	0.22	0.14	
<i>f</i> _e ^a				
<i>ABCB1</i> CGC/CGC	0.50 \pm 0.09	0.55 \pm 0.08	1.14 (0.89-1.39)	0.25
<i>ABCB1</i> CGC/TTT	0.50 \pm 0.06	0.47 \pm 0.10	0.96 (0.81-1.11)	0.44
<i>ABCB1</i> TTT/TTT	0.62 \pm 0.22	0.56 \pm 0.16	0.96 (0.78-1.14)	0.41
P value, between diplotype groups	0.44	0.36	0.24	
<i>t</i> _{1/2} (h)				
<i>ABCB1</i> CGC/CGC	7.3 \pm 3.0	6.2 \pm 1.5	0.94 (0.70-1.17)	0.26
<i>ABCB1</i> CGC/TTT	7.7 \pm 2.5	7.3 \pm 2.4	0.98 (0.78-1.17)	0.51
<i>ABCB1</i> TTT/TTT	7.3 \pm 2.3	7.4 \pm 1.9	1.04 (0.90-1.17)	0.65
P value, between diplotype groups	0.82	0.16	0.49	

^a*f*_e and CL_R could not be calculated for three subjects (n=2, CGC/CGC; n=1, CGC/TTT). Data are expressed as arithmetic mean \pm standard deviation or mean relative change (95% CI). Relative change=(sitagliptin + atorvastatin)/sitagliptin alone.

ABCB1 CGC/CGC, n=9; *ABCB1* CGC/TTT, n=10; *ABCB1* TTT/TTT, n=10.

Table 3

Single-dose sitagliptin pharmacokinetics in the absence and presence of atorvastatin (n=29)

Pharmacokinetic parameter	Sitagliptin Geometric Mean (90% CI)	Sitagliptin + Atorvastatin Geometric Mean (90% CI)	GMR (90% CI)	P value
C _{max} (ng/ml)	399 (352, 451)	371 (326, 424)	0.93 (0.86, 1.01)	0.16
AUC _{0-∞} (ng*h/ml)	3218 (2865, 3614)	3082 (2696, 3522)	0.96 (0.91, 1.01)	0.15
CL _R ^a (ml/min)	254 (215, 300)	259 (225, 298)	1.02 (0.93, 1.12)	0.69
f _e ^a	0.52 (0.47, 0.58)	0.51 (0.47, 0.56)	0.98 (0.90, 1.06)	0.68
t _{1/2} (h) ^b	7.4 ± 2.5	7.0 ± 2.0	-	0.39

^aCL_R and f_e could not be calculated for three subjects due to missing urine samples or incomplete urine collection

^barithmetic mean ± standard deviation. GMR=geometric mean ratio; CI=confidence interval.

Table 4

Atorvastatin and atorvastatin metabolite pharmacokinetics by *ABCB1* diplotype group.

<i>ABCB1</i> Diplotype	Pharmacokinetic Parameters		
	C _{max} (ng/ml)	AUC _{tau} (ng*h/ml)	T _{1/2} (h)
Atorvastatin			
CGC/CGC	8.6 ± 6.2	44.4 ± 28.0	5.7 ± 1.2
CGC/TTT	7.5 ± 7.6	35.4 ± 35.6	6.9 ± 2.0
TTT/TTT	10.6 ± 7.4	49.0 ± 37.1	6.4 ± 2.1
P value, between diplotype groups	0.43	0.29	0.55
Atorvastatin lactone			
CGC/CGC	11.0 ± 11.9	87.3 ± 69.3	7.0 ± 2.5
CGC/TTT	7.4 ± 4.7	69.8 ± 54.7	6.7 ± 2.3
TTT/TTT	13.8 ± 11.2	101.0 ± 64.2	9.2 ± 6.0
P value, between diplotype groups	0.23	0.35	0.66
2-hydroxyatorvastatin			
CGC/CGC	5.5 ± 3.4	43.2 ± 21.6	6.3 ± 2.7
CGC/TTT	5.1 ± 4.1	45.0 ± 38.7	7.5 ± 3.0
TTT/TTT	4.5 ± 2.3	38.6 ± 19.5	7.0 ± 1.5
P value, between diplotype groups	0.93	0.93	0.32
2-hydroxyatorvastatin lactone			
CGC/CGC	4.4 ± 3.5	37.3 ± 22.5	6.8 ± 1.8
CGC/TTT	4.1 ± 3.0	42.6 ± 31.1	7.8 ± 4.2
TTT/TTT	3.9 ± 1.9	38.5 ± 19.3	9.9 ± 8.5
P value, between diplotype groups	0.98	0.96	0.92
4-hydroxyatorvastatin			
CGC/CGC	0.48 ± 0.61	4.6 ± 4.6	14.2 ± 4.3
CGC/TTT	0.25 ± 0.14	3.2 ± 1.6	19.3 ± 12.9
TTT/TTT	0.39 ± 0.34	5.1 ± 4.5	12.6 ± 5.2
P value, between diplotype groups	0.61	0.61	0.29
4-hydroxyatorvastatin lactone			
CGC/CGC	0.84 ± 0.11	9.1 ± 10.2	10.5 ± 5.5
CGC/TTT	0.7 ± 0.43	7.2 ± 4.0	12.8 ± 4.3
TTT/TTT	0.91 ± 0.64	10.4 ± 7.0	14.5 ± 8.8
P value, between diplotype groups	0.63	0.46	0.29

ABCB1 CGC/CGC, n=9; *ABCB1* CGC/TTT, n=10; *ABCB1* TTT/TTT, n=10. Data are expressed as arithmetic mean ± standard deviation.