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SLCO1B1 521T→C functional genetic polymorphism and lipid-lowering efficacy of multiple-dose pravastatin in Chinese coronary heart disease patients

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What is already known about this subject

- Both oral clearance as well as delivery of pravastatin to its molecular targets in hepatocytes are greatly influenced by the organic anion transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1.*
- The role of genetic factors that determine the marked interindividual variability in lipid-lowering efficacy of pravastatin in Chinese patients is not known.
- The present study was designed to evaluate the impact of a common functional genetic polymorphism in *SLCO1B1* (521T→C: Val174Ala) on pravastatin efficacy in Chinese patients with coronary heart disease.

What this study adds

521T→C functional genetic polymorphism of *SLCO1B1* is significantly associated with an attenuated total cholesterol-lowering efficacy of pravastatin in Chinese patients with coronary heart disease.

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Aims

Pravastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, which is widely used both in primary and secondary prevention of coronary heart disease (CHD). Pravastatin is not subject to metabolism by cytochrome P450s, but it is actively transported from blood into target tissues (e.g. hepatocytes in the liver) by the organic anion transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1.* The aim of the present study was to evaluate the impact of *SLCO1B1* 521T→C (Val174Ala) functional genetic polymorphism on the lipid-lowering efficacy of multiple-dose pravastatin in Chinese patients with CHD.

Methods

Forty-five hospitalized patients with CHD prospectively received pravastatin as a single-agent therapy (20 mg day^{-1} p.o.) for 30 days. Serum triglycerides, total cholesterol, low-density lipoprotein-cholesterol and high-density lipoprotein-cholesterol concentrations were determined before and after pravastatin treatment.

Results

Pravastatin treatment significantly decreased plasma lipids in all patients ($P < 0.001$). Importantly, we showed an attenuated pravastatin pharmacodynamic effect on total cholesterol in patients with 521TC heterozygote genotype (from 5.52 ± 0.51 mmol l^{-1} to 4.70 ± 0.35 mmol l^{-1}, % change −14.5 ± 6.6%, $N = 9$) compared with 521TT homozygote genotype (from 5.47 ± 1.15 mmol l^{-1} to 4.21 ± 0.89 mmol l^{-1}, % change −22.4 ± 10.3%, $N = 36$) (mean ± SD, $P = 0.03$, two-tailed test with α set at 5%). *SLCO1B1* 521T→C functional polymorphism did not significantly influence pravastatin pharmacodynamics on other plasma lipids ($P > 0.05$).

Conclusions

The 521T→C polymorphism of *SLCO1B1* appears to modulate significantly the total cholesterol-lowering efficacy of pravastatin in Chinese patients with CHD. Further studies are warranted to determine the extent to which *SLCO1B1* genetic variation may contribute to resistance to pravastatin in Asian patients treated with standard doses of pravastatin.

Introduction

Pravastatin, one of the 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (statins), is widely used in the treatment of hypercholesterolaemia. Pravastatin is prescribed both for the primary and secondary prevention of coronary heart disease (CHD) [1–3]. However, there is marked interindividual variability in therapeutic response to pravastatin. A deeper understanding of the mechanisms mediating attenuated response or treatment failure [4] associated with pravastatin therapy in different human populations is essential for individualization of preventive antilipidaemic interventions and reducing the global public health burden of CHD.

After an oral dose, pravastatin is rapidly absorbed from the small intestine and then taken up rapidly and selectively from the portal circulation into the liver through a sodium-independent bile acid transporter, the organic anion transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1* [5–7]. OATP1B1 plays an important role in the hepatic uptake of many endogenous and foreign chemicals as well as drugs such as pravastatin, rosuvastatin, pitavastatin, atorvastatin, atrasentan and repaglinide [8–12]. *SLCO1B1* gene displays a number of single nucleotide polymorphisms (SNPs) that cause impaired transporter activity [13–16]. For example, clinical pharmacokinetic investigations *in vivo* have determined that *SLCO1B1*15* haplotype is associated with a significant reduction in oral clearance of a single dose of pravastatin [13]. Consistent with this, *SLCO1B1*5* (521T→C), **15* (388A→G and 521T→C) and **17* (−11187G→A, 388A→G and 521T→C) haplotypes result in increased systemic exposure of pravastatin [14–16]. Importantly, the 521T→C genetic variation is the predominant and shared key SNP in determining the functional impact of *SLCO1B1*5*, **15* and **17* haplotypes on OATP1B1 transporter function [13–16].

Because the uptake and delivery of pravastatin into hepatocytes by OATP1B1 is a crucial prerequisite step for its therapeutic efficacy, it is reasonable to postulate that interindividual differences in intracellular pravastatin exposure in hepatocytes can modulate, in part, its cholesterol-lowering efficacy. Therefore, subjects who carry the key functional 521T→C SNP (associated with impaired transporter activity) in *SLCO1B1* may exhibit decreased intracellular pravastatin concentration and, by extension, an attenuated pharmacodynamic effect on cholesterol levels. The aim of the present study was to evaluate the role of *SLCO1B1* 521T→C genetic variation in relation to the lipid-lowering efficacy of multiple-dose pravastatin in Chinese patients with CHD.

Materials and methods

Subjects

The study was approved by the Research Ethics Committee of the Xiangya School of Medicine, Central South University. All subjects provided written, informed consent in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). A total of 45 stable CHD inpatients with or without hyperlipidaemia were enrolled (17 females, 28 males; age range 41–78 years). They had initial coronary angiograms and significant coronary stenosis (>40% luminal narrowing) as defined by coronary angiography. None of the subjects had taken HMG-CoA reductase inhibitors (statins) previously and all strictly abstained from smoking, alcohol and caffeine during treatment in hospital. Subjects with diabetes mellitus, liver or renal failure, dropsical nephritis, liver or kidney transplantation were excluded from participation in the study. To prevent the potential confounding effect of concomitant medications on plasma lipid concentrations or OATP1B1 transporter activity, patients who had taken any other lipid-lowering drugs, ciclosporin, rifampicin, methotrexate, fexofenadine, caspofungin, irinotecan or flavanoids in the previous 2 months were also excluded.

Study design

Investigators and participants were blind to genotype data during collection of the phenotypic data. Similarly, genotyping was performed blind to the phenotypic data. All subjects were asked to take low-fat diet and prospectively treated with an oral 20-mg daily dose of pravastatin at 21.00 h before bedtime for 30 consecutive days. Blood samples were collected at baseline before the first dose of pravastatin (study day 0) and on study day 30, prior to breakfast.

Genotyping for SLCO1B 1521T→C functional polymorphism

Genomic DNA was extracted by a standard manual chloroform–phenol extraction procedure. An amplification refractory mutation system (ARMS-PCR) was used for 521T→C genotype analysis as previously described [17].

Measurement of plasma lipid levels

Measurement of plasma lipids concentrations was performed in a hospital laboratory. Total and high-density lipoprotein (HDL)-cholesterol and triglyceride concentrations in the plasma were determined by use of standard, automated methods (Hitachi 747, Tokyo, Japan). The low-density lipoprotein (LDL)-cholesterol was calculated by the Friedewald formula [18].

Table 1
Baseline characteristics of study subjects before pravastatin treatment

Characteristic	*SLCO1B1* 521TT group ($n = 36$)	*SLCO1B1* 521TC group ($n = 9$)	*P*-value
Age (years)	65.8 ± 11.2	66.3 ± 8.81	0.70
Sex (M/F)	22/14	6/3	–
Body mass index (kg m^{-2})	25.49 ± 3.45	24.78 ± 2.65	0.54
Medication			
Aspirin	29 (81%)	7 (78%)	0.85
β-blocker	25 (69%)	6 (67%)	0.87
Calcium antagonists	17 (47%)	5 (56%)	0.66
Angiotensin-converting enzyme inhibitors	22 (61%)	5 (56%)	0.76
Nitrates	20 (56%)	6 (67%)	0.55
Clopidogrel	15 (42%)	3 (33%)	0.65
Total cholesterol (mmol l^{-1})	5.47 ± 1.15	5.52 ± 0.51	0.11
LDL-cholesterol (mmol l^{-1})	3.67 ± 0.91	3.63 ± 0.15	0.64
HDL-cholesterol (mmol l^{-1})	1.15 ± 0.37	1.01 ± 0.35	0.76
Triglycerides (mmol l^{-1})	1.96 ± 0.85	2.34 ± 1.66	0.12

Data are shown as mean ± SD. LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

Statistical analysis

Statistical analyses were performed with SPSS software (version 11.0 for Windows; SPSS Inc., Chicago, IL, USA). Hardy–Weinberg equilibrium was assessed with a χ^2 test of goodness-of-fit in the study sample. Paired Student's *t*-test was performed for the lipid concentrations before and after pravastatin treatment. An unpaired Student's *t*-test was used to compare the differences in the degree of reduction in plasma concentrations between the two SLCO1B1 genotypic groups. A two-sided test with type error level (α) set at 5% was used in all statistical analyses. Data were presented as mean ± SD. A two-tailed P-value < 0.05 was considered to be statistically significant for all analyses.

Results

Pravastatin was well tolerated by all patients. No subject showed any elevation of aminotransferase or creatine phosphokinase after treatment, and no subjects reported skeletal muscle abnormalities or other notable safety concerns during the study. After *SLCO1B1* 521T→C genotyping, nine patients were identified with 521T→C heterozygote genotype with the remaining of the 36 subjects displaying the 521TT homozygous genotype. The allele frequency of the 521C allele was 10% in our sample of Chinese individuals. The genotype frequencies were in Hardy–Weinberg equilibrium. Baseline characteristics of the two *SLCO1B1* genotypic panels are presented in Table 1.

After pravastatin treatment for 30 days, total cholesterol, LDL-cholesterol and triglyceride concentrations were decreased from baseline, on average, by 20.9 ± 10.1%, 27.5 ± 14.4% and 18.1 ± 22.6%, respectively (Figure 1) ($P < 0.001$). HDL-cholesterol was not significantly affected after pravastatin treatment (Figure 1).

We found a significant influence of *SLCO1B1* genotype on percentage reduction in total cholesterol from baseline after pravastatin treatment. The group of patients with a 521TC heterozygous genotype showed, on average, a 14.5 ± 6.6% (SD) reduction in total cholesterol, whereas patients with 521TT homozygous genotype displayed a 22.4 ± 10.3% reduction from baseline ($P = 0.03$) (Figure 2 and Table 2). On the other hand, the degree of change in plasma LDL-cholesterol, HDL-cholesterol and triglyceride concentrations did not show a significant difference between 521TT and 521TC genotypes (Figure 2 and Table 2).

Discussion

Cholesterol-lowering therapy is a crucial step in the primary and secondary prevention of CHD and other cardiovascular diseases. Although pravastatin is a widely prescribed HMG-CoA reductase inhibitor for the

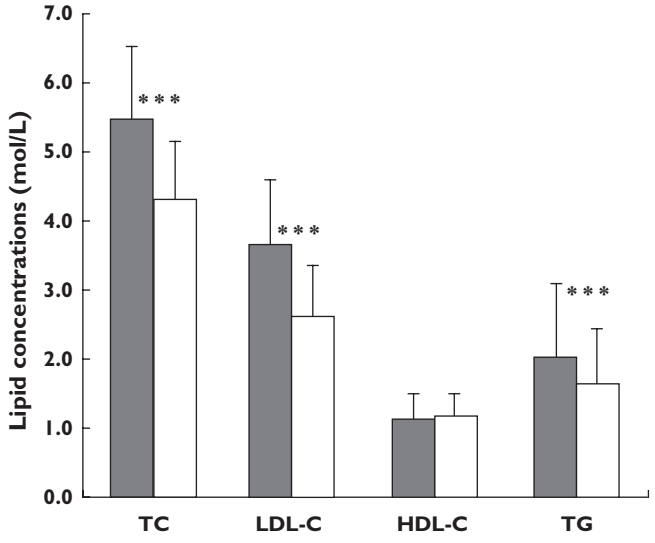

Figure 1

Total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglyceride (TG) concentrations (mmol l^{-1}) at baseline (■) and after treatment with 20 mg pravastatin daily for 30 days (□) in 45 patients with coronary heart disease. Data are shown as mean ± SE. ***P-value < 0.05

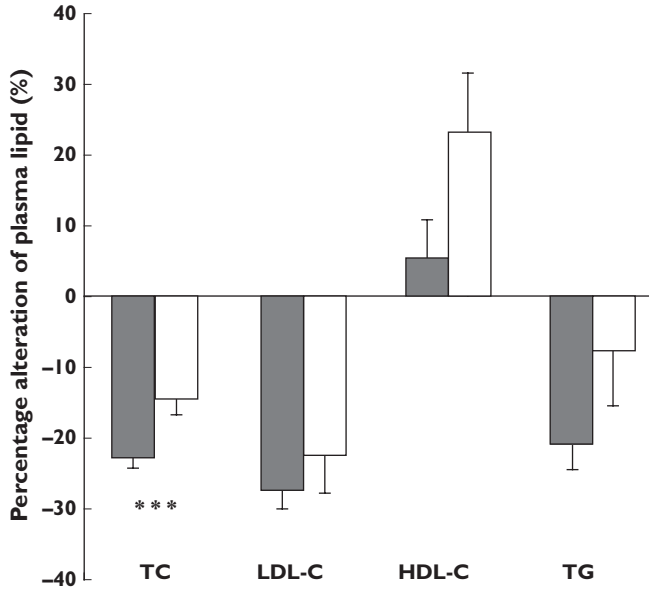

Figure 2

Comparison of percentage changes from baseline in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglyceride (TG) between the SLCO1B1 reference genotype group (521TT, ■) and those who carry the 521C allele (521TC genotype, □). Data are shown as mean ± SE. ***P-value < 0.05

treatment of hypercholesterolaemia, it displays marked interindividual variability in lipid-lowering efficacy [19]. The mechanism(s) of individual differences in pravastatin pharmacodynamics remains largely unknown.

The dosage of pravastatin used in clinical practice ranges from 10 mg day^{-1} to 80 mg day^{-1}. Previous studies have indicated that 10 mg day^{-1} cannot attain sufficient lipid-lowering efficacy and is seldom used in lipid-lowering treatment. Meanwhile, there is little difference in the lipid response to pravastatin between daily doses of 20 mg and 40 mg [20, 21]. Moreover, it has been reported that pravastatin therapy for 4 weeks in patients with hyperlipidaemia is sufficient to decrease the total cholesterol level by 17–24% and LDL-cholesterol levels by 23–35% [22]. For the above reasons, in this study all patients had taken pravastatin 20 mg day^{-1} for 30 days.

Pravastatin is not subject to metabolism by cytochrome P450s. The disposition of pravastatin is significantly influenced by OATP1B1 expressed in the basolateral (sinusoidal) membrane of hepatocytes [23, 24]. After oral administration, pravastatin is actively transported by OATP1B1 from blood into hepatocytes and subsequently excreted into the bile as an unchanged compound. Hence, it is conceivable that genetic and/or environmental factors that impair pravastatin delivery to its intracellular drug targets (e.g. HMG-CoA reductase) in hepatocytes may explain treatment failure or partial response to pravastatin in some patients. Consistent with this postulation, we found in our study that the *SLCO1B1* 521T→C polymorphism carriers (521TC genotype) showed attenuated total cholesterol-lowering effect compared with those with the 521TT genotype. Presumably, this may be a consequence of a decreased intracellular concentration of pravastatin. However, the percentage reduction of LDL-cholesterol was not found significantly different between the groups. Because the subjects were recruited without knowing their genotypes, and after genotype assay, the TT homozygotes ($n = 36$) were four times more prevalent than the CT heterozygotes ($n = 9$). This affected sample power, which is only 80%, which presumably explains the significant positive result only with total cholesterol but not LDL-cholesterol.

The prospective design of the present study and exclusion of subjects with concomitant medications that may interfere with OATP1B1 activity reduced the risk for confounding by environmental factors and drug-drug interactions, which lend further support to the association observed with the functional *SLCO1B1* polymorphism. This finding is also consistent with previous

Table 2
Comparison of changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride between *SLCO1B1* 521TT and 521TC genotypic groups after treatment with 20 mg pravastatin daily for 30 days

	Genotype group (*N*)	Baseline (mmol l^{-1})	After pravastatin (mmol l^{-1})	Mean % change (95% CI)	*P*
Total cholesterol	TT (36)	5.47 ± 1.15	4.21 ± 0.89	–22.4 (–25.9, –19.0)	0.03
	TC (9)	5.52 ± 0.51	4.70 ± 0.35	–14.5 (–19.6, –9.4)	
LDL-cholesterol	TT (36)	3.67 ± 0.91	2.60 ± 0.74	–27.5 (–31.9, –23.2)	0.33
	TC (9)	3.63 ± 1.05	2.72 ± 0.67	–22.3 (–34.1, –10.6)	
HDL-cholesterol	TT (36)	1.15 ± 0.37	1.15 ± 0.37	5.3 (–6.3, 16.9)	0.15
	TC (9)	1.01 ± 0.35	1.19 ± 0.25	23.1 (3.8, 42.4)	
Triglyceride	TT (36)	1.96 ± 0.85	1.51 ± 0.66	–20.7 (–28.2, –13.3)	0.12
	TC (9)	2.34 ± 1.66	1.98 ± 1.17	–7.7 (–25.3, 9.8)	

N, Sample size in each genotypic group; 95% CI, 95% confidence interval. Data are shown as mean ± SD. P-value, Significant difference of lipid-lowering effect (% change) of pravastatin in 521T→C variants by unpaired t-test. LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

reports on pravastatin pharmacokinetics. For example, 521T→C variant, the predominant SNP shared by *SLCO1B1*5* and *SLCO1B1*15* haplotypes, was associated with an increased pravastatin plasma concentration [13–15]. This is probably due to impaired uptake of pravastatin into hepatocytes by OATP1B1 encoded by carriers of the 521C allele. In a previous study by our group, we have shown that the *SLCO1B1* 521C allele may result in increased plasma concentrations of another OATP1B1 substrate (antidiabetic agent nateglinide) in healthy Chinese volunteers [17].

In a multiple-dose clinical pharmacokinetic study of healthy subjects, there was a 110% increase in pravastatin AUC in subjects with the *SLCO1B1* variant haplotype carrying the 521C allele [23]. Moreover, there was a nonsignificant finding for a *SLCO1B1* genotype effect on the lipid-lowering efficacy of pravastatin (40 mg day^{-1}) after 3 weeks: the average percentage decrease in total cholesterol concentration was 13.1 ± 9.1% and 19.1 ± 8.3% in the variant and control groups, respectively ($P = 0.19$). It is noteworthy that the attenuated lipid-lowering efficacy of pravastatin in the presence of 521C allele may be less discernible in healthy subjects compared with CHD patients who have high plasma cholesterol. *SLCO1B1* genotype effect on plasma lipids may also require pravastatin treatment for >3 weeks. In the same study, treatment with pravastatin for 3 weeks was associated with a 27.7% decrease in LDL-cholesterol in volunteers with impaired OATP1B1 activity (carriers of 521C). The sample size was small in this study, but it indicates that *SLCO1B1* polymorphism may not necessarily be the major determinant in nonresponse to pravastatin [23]. In a retrospective study conducted in another Asian population, 66 Japanese hypercholesterolaemia patients under treatment with OATP1B1 substrate drugs pravastatin, simvastatin or atorvastatin, *SLCO1B1* 521TT genotype was associated with a higher total cholesterol-lowering effect [25]. This is in accordance with the findings of the present prospective study in Chinese patients with CHD.

In summary, the 521T→C polymorphism of *SLCO1B1* appears to modulate the total cholesterol-lowering efficacy of pravastatin treatment in Chinese CHD patients. We caution that the finding of an attenuated cholesterol-lowering efficacy in patients who carry the *SLCO1B1* 521C allele needs to be replicated in larger prospective cohorts of patients in China and other Asian populations. Moreover, it remains to be determined whether and to what extent *SLCO1B1* 521T→C polymorphism influences pravastatin efficacy on plasma lipids other than cholesterol during longer term (>1 month) treatment at different dose ranges. On the other hand, cardiovascular diseases continue to impose a large global public health burden. Genetic testing that is helpful in identifying subpopulations at risk for treatment failure to antilipidaemic agents may open an avenue for early therapeutic interventions in the form of genotype-guided individualized dosing of pravastatin or presumably, genotype-directed coadministration of

OATP1B1 inducers to augment pravastatin delivery to target tissues.

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