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The effect of Na^+/taurocholate cotransporting polypeptide (NTCP) c.800C > T polymorphism on rosuvastatin pharmacokinetics in Chinese healthy males

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This study was designed to investigate the potential association between NTCP c.800C > T polymorphism and rosuvastatin pharmacokinetics in Chinese healthy males. 305 individuals were enrolled to identify NTCP c.800C > T, OATP1B1 c.521T > C and BCRP c.421C > A genotypes by direct sequencing and pyrosequencing methods, respectively. 17 healthy volunteers who were OATP1B1 c.521TT and BCRP c.421CC wild-type homozygotes with different NTCP c.800C > T genotype were selected to participate in this pharmacokinetic study. Nine were NTCP c.800CC wild-type homozygotes and the other eight subjects were carriers with at least one c.800T variant allele (seven subjects with c.800CT genotype and one was homozygote of c.800TT). All the subjects received a single oral dose of 10 mg rosuvastatin. The plasma concentrations of rosuvastatin were measured up to 72 h by a LC-MS method. NTCP c.800C > T genetic polymorphism markedly effected rosuvastatin pharmacokinetics. The $AUC_{(0–72)}$ and $AUC_{(0\rightarrow\infty)}$ in subjects with NTCP c.800CT + TT genotype were 56% (162.64 ± 37.55 *vs.* 103.99 ± 28.15 ng.h/ml, $P = 0.016$) and 57% greater (178.51 ± 42.75 *vs.* 113.60 ± 33.73 ng.h/ml, $P = 0.020$) than those in the c.800CC wild-type subjects, respectively. In the c.800CT + TT mutant group, the C_{max} was about 78% higher than those in c.800CC genotype (14.31 ± 3.63 *vs.* 8.04 ± 1.72 ng.h/ml, $P = 0.004$). The oral clearance (CL/*F*) of rosuvastatin in subjects with the c.800CT + TT genotype was only 63% of those in the c.800CC genotype (58.32 ± 12.16 *vs.* 93.04 ± 20.61 ng.h/ml, $P = 0.009$). The half-time ($T_{1/2}$) and the T_{max} had no significant difference between two groups ($p = 0.466$ and 0.713, respectively). NTCP c.800C > T polymorphism play a critical role in the individual variability of rosuvastatin pharmacokinetics in Chinese healthy males after excluding the impact of OATP1B1 c.521T > C and BCRP c.421C > A polymorphisms.

1. Introduction

Rosuvastatin, an efficient hydroxymethylglutaryl coenzyme A reductase (HMG-CoA) inhibitor, is a widely used lipid-lowering agent to treat hyperlipidemia. Rosuvastatin is subject to very limited biotransformation and only about ~10% rosuvastatin is recovered as metabolites mainly by CYP2C9 (Carswell et al. 2002). Carrier-mediate transport plays an important role in rosuvastatin disposition. Accumulated data suggest that OATP1B1 (gene *SLCO1B1*) and BCRP (gene $ABCG_2$) are two key transporters responsible for rosuvastatin uptake and efflux, respectively (Romaine et al. 2009; Huang et al. 2006). Thereby, functional genetic polymorphisms in these two transporters could be the potential for the individual difference in rosuvastatin pharmacokinetics and therapeutic efficacy. A growing evidence indicated that OATP1B1 c.521T > C and BCRP c.421C > A, two loss-of-function variants with totally impaired transport activity for statins, resulted in elevated plasma concentration of rosuvastatin (Choi et al. 2008; Pasanen et al. 2007; Keskitalo et al. 2009; Zhang et al. 2006). In a previous pharmacokinetic study, it was reported that subjects with OATP c.521CT and TT genotypes displayed a 1.7-fold increase in rosuvastatin concentration compared with those in wild-type individuals (Pasanen et al. 2007). On the other hand, BCRP c.421C > A mutation was observed to associate with almost 2-fold higher plasma concentration of rosuvastatin in both Asians and Caucasians (Zhang et al. 2006; Keskitalo et al. 2009).

Na^+/taurocholate cotransporting polypeptide (NTCP; gene *SLC10A1*), exclusively located on the basolateral membrane of the hepatocytes, is one of most important transporters to maintain bile acid homeostasis (Craddock et al. 1998; Hagenbuch and Meier 1996). NTCP mediates ~80% taurocholate uptake in a sodium-coupled way at the ratio of $2Na^+$:1 taurocholate stoichiometry (Hagenbuch and Meier 1996). Although identified as a liver-specific bile acid carrier, it is capable of transporting some non-bile acid substrates like estrone sulfate (Craddock et al. 1998). A study demonstrated that a considerable part of rosuvastatin hepatic uptake (~35%) happened in a sodium-

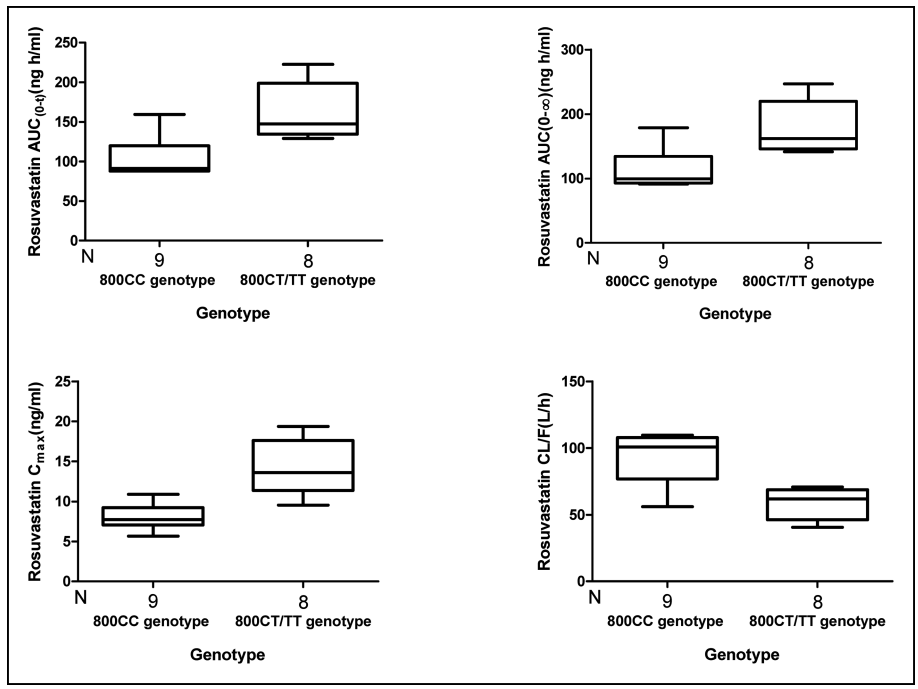

Fig. 1: NTCP c.800C > T genotype and the main pharmacokinetic parameters of a single dose of 10 mg rosuvastatin. Bars represent interquartile range, and lines across bars represent mean. NTCP c.800CC genotype group (n = 9), NTCP c.800CT + 800TT genotype group (n = 8). Data are expressed as mean ± S.D.

dependent way, and this process could be apparently suppressed by cyclosporine, a well-known potent NTCP inhibitor, strongly suggesting that NTCP was involved in rosuvastatin uptake (Ho et al. 2006). Recently, *in vitro* kinetic analysis revealed that cells transfected with human-NTCP cRNA or expression plasmid showed a significant uptake of rosuvastatin compared with the control group, confirming that rosuvastatin was a substrate of NTCP (Choi et a. 2011; Pan et al. 2011). Nowadays, serval functional mutations have been identified in the *SLC10A1* gene and the frequency of these polymorphisms was characterized by remarkable ethnicity-dependent difference (Ho et al. 2004). Among them, NTCP c.800C > T (rs2296651, NTCP*2) was identified as an Asian-specific polymorphism with a 7.5% frequency of c.800T variant allele for Chinese (Ho et al. 2004; Pan et al. 2011). It was suggested that this mutation localized in a critical region for bile acids recognition and displayed a near complete loss of function for bile acids uptake (Ho et al. 2004; Pan et al. 2011). Remarkably, *in vitro* kinetic analysis revealed NTCP c.800C > T mutation displayed a significant increase of intrinsic clearance for rosuvastatin (in terms of V_{max}/K_m) compared with wild-type, which indicated that NTCP c.800C > T mutation was associated with a profound increase of transport ability of rosuvastatin (Ho et al. 2006; Pan et al. 2011).

Given the important role of NTCP plays in rosuvastatin disposition, c.800C > T mutation also could be a potential reason for the inter-subject variability of rosuvastatin pharmacokinetics. However, the clinical implication of NTCP c.800C > T polymorphism on rosuvastatin pharmacokinetics still remained unknown. The purpose of the present study was to investigate the potential impact of NTCP c.800C > T polymorphism on rosuvastatin pharmacokinetics in Chinese healthy males excluding the effects of OATP1B1c.521T > C and BCRP c.421C > A polymorphisms.

2. Investigations and results

2.1. NTCP c.800C > T allele frequency in Chinese healthy population

Genetic analysis for NTCP c.800C > T, OATP1B1 c.521T > C and BCRP c.421C > A polymorphisms were successfully done in the all 305 Chinese healthy volunteers. As the result, the frequencies of the NTCP c. 800C and c. 800T alleles were found to be 92.8% and 7.2%, respectively. The frequency of c.800CC genotype was 86.1%; that of the c.800CT genotype, 13.3%; and that of c.800TT genotype, 0.6%. The observed frequencies of NTCP c.800C > T polymorphism were in accordance with Hardy-Weinberg equilibrium.

2.2. Effect of NTCP c.800C > T polymorphism on rosuvastain pharmacokinetics

The main pharmacokinetic parameters of rosuvastatin in different NTCP genotype groups were summarized in the Table and Figure 1. The mean $AUC_{(0–72h)}$ and $AUC_{(0–\infty)}$ of rosuvastatin in subjects with the c.800CT + TT genotypes were about 56% ($P = 0.016$) and 57% greater ($P = 0.020$) than those with the c.800CC genotype, respectively; and the C_{max} was about 78% higher than that in c.800CC genotype ($P = 0.004$). In subjects with the c.800CT + TT mutant group, the oral clearance (CL/*F*) of rosuvastatin was only about 63% of that in the c.800CC wild-type group ($P = 0.009$). The elimination half-time ($T_{1/2}$) and

Table: Pharmacokinetic parameters of single oral dose of 10 mg rosuvastatin in healthy Chinese Han males with different NTCP c.800C > T genotypes

	800CC (N = 9)	800CT + TT (N = 8)	*P* value
$AUC_{0–72}$ (ng·h/ ml)	103.99 ± 28.15	162.64 ± 37.55	0.016
$AUC_{0-\infty}$ (ng·h/ ml)	113.60 ± 33.73	178.51 ± 42.75	0.020
C_{max}(ng/ml)	8.04 ± 1.72	14.31 ± 3.63	0.004
$T_{1/2}$(h)	18.12 ± 2.06	17.18 ± 1.98	0.466
T_{max} (h)	4.00 ± 0.89	3.80 ± 0.84	0.713
CL/*F*(l/h)	93.04 ± 20.61	58.32 ± 12.16	0.009

Data are expressed as mean ± S.D.

$AUC_{(0\rightarrow\infty)}$, mean total area under the plasma concentration–time curve from time 0 to∞; $AUC_{(0–72)}$, mean total area under the plasma concentration–time curve from time 0 to72 h; C_{max}, peak plasma concentration; T_{max}, time to peak plasma concentration; $T_{1/2}$, terminal elimination half-life; CL/*F*, oral clearance

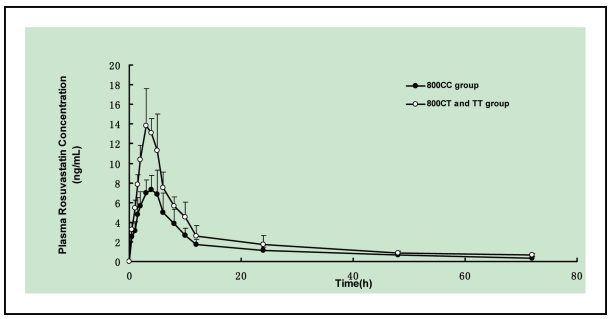

Fig. 2: The curve of time – concentration of rosuvastatin in 17 healthy volunteers with different NTCP c.800C > T genotypes after administrated a single oral dose of 10 mg rosuvastatin. Solid rounds represent NTCP c.800CC genotype group (n = 9); open rounds represent NTCP c.800CT + 800TT genotype group (n = 8). Data are expressed as mean ± S.D.

the T_{max} of rosuvastatin had no significant difference between two groups ($p = 0.466$ and 0.713, respectively). Figure 2 shows the time–concentration curves of rosuvastatin between two different NTCP c.800C > T genotype groups. The $AUC_{(0-\infty)}$ of rosuvastatin was higher in the NTCP c.800CT + TT group than that in the c.800CC group. The C_{max} was also increased in the c.800CT + TT group compared to that in the c.800CC group.

3. Discussion

The aim of present study was to access the association between NTCP c.800C > T polymorphism and rosuvastatin pharmacokinetics in Chinese healthy males. Our results illustrated that the disposition of rosuvastatin was significantly affected by NTCP c. 800C > T polymorphism after exclusion of OATP1B1 c.521T > C and BCRP c.421C > A mutations. Subjects with c.800CT and TT genotypes exhibited a markedly higher systemic exposure of rosuvastatin than those with wild-type genotype.

Recent *in vitro* studies indicated that NTCP-mediate uptake was involved in rosuvastatin disposition and NTCP c.800C > T mutation exhibited an enhanced transport activity of rosuvastatin (Ho et al. 2006; Choi et al. 2011; Pan et al. 2011). Rosuvastatin underwent little metabolism mainly by CYP2C9. Increasing evidence illustrated it was a good substrate for OATP1B1 and BCRP. Since multiple pathways were involved in rosuvastatin uptake, redundancy of transport capacity for rosuvastatin could influence the *in vivo* functional effect of NTCP c.800C > T polymorphism on rosuvastion disposition. In order to get a better understanding of the association between NTCP c.800C > T variant alone and rosuvastatin pharmacokinetics in human beings, in this study we excluded OATP1B1 c.521T > C and BCRP c.421C > A polymorphisms, two major determinants with increasing plasma concentration of rosuvastatin due to their almost abolished transport activity.

In our study, we observed a 57% greater $AUC_{(0-\infty)}$ and almost 78% higher C_{max} in subjects with c.800CT and TT genotype compared to those of c.800CC wild-type subjects, which clearly demonstrated a substantial reduction of uptake capacity of NTCP c.800C > T variant for rosuvastatin *in vivo*. *In vitro* kinetic studies illustrated NTCP was a high-capacity transporter

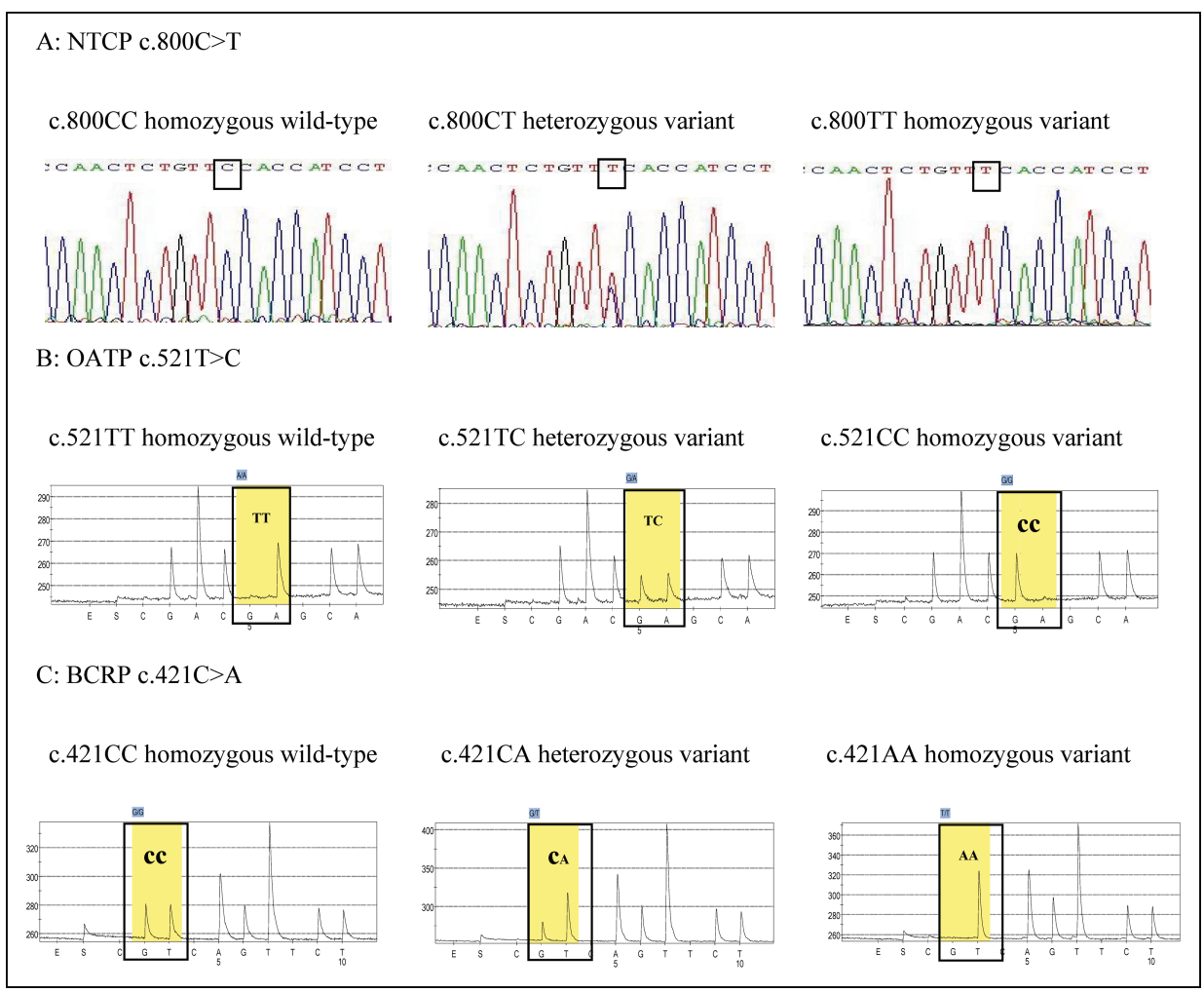

Fig. 3: Determination of NTCP c.800C > T, OATP1B1 c.521T > C and BCRP c.421C > A polymorphisms by direct sequencing and pyrosequencing method, respectively.

for rosuvastatin but its affinity for rousuvastatin was significantly lower than those of its endogenous substrates such as taurocholate and estrone sulfate (Ho et al. 2004, 2006; Pan et al. 2011). It was reported that the K_m values of NTCP to rosuvastatin were markedly higher than those of taurocholate, irrespective of c.800C > T mutation or not (Pan et al. 2011). Thereby, the affinity of NTCP c.800C > T mutation for rosuvastatin was still lower than those for taurocholate even though its capacity to transport taurocholate was almost abolished. Moreover, uptake ability of NTCP c.800C > T mutation for estrone sulfate was essentially equivalent to those of wild-type (Ho et al. 2004). It was therefore assumed that these endogenous substrates would be potential (non)competitive inhibitors for NTCP-mediate rosuvastatin uptake. The previously observed function-gain uptake ability of c.800C > T mutation for rosuvastatin in cellular assays was obtained in the absence of any endogenous substrates, which was obviously inconsistent with the physical conditions in human beings. Interestingly, a recent study by Lee et al. reported that c.800C > T polymorphism was associated with a relatively higher rosuvastatin plasma concentration only in patients with one or two copies of OATP1B1 c.521T > C variant (Lee et al. 2013). Although without statistical difference, this could implied that subjects carrying NTCP c.800C > T mutation were accompanied with a decrease capacity of rousvastatin uptake *in vivo*, in accordance with our observations.

Previous studies showed that plasma concentrations of rosuvastatin were approximately 2-fold higher in east Asians than those in Caucasians (Lee et al. 2005; Tzeng et al. 2008). This ethnicity-related difference of rosuvastatin pharmacokinetics could be partly explained by the significantly higher frequency of BCRP c.421A allele in Asians than those in Caucasians (∼35% vs.∼14%., respectively) (Zamber et al. 2003). Similarly, it is reasonable to assume that NTCP c.800C > T mutation, an Asian-specific allele, could be a new genetic factor responsible for the ethnic variability of rosuvastatin plasma concentration based on our results. Moreover, these pharmacokinetic data corresponded well to the results form JUPITER study that Caucasians with BCRP c.421A allele displayed a better response to rosuvastatin therapy (Chasman et al. 2012). However, data about the impact of NTCP c.800C > T mutation on rosuvastatin pharmacokinetics and therapeutic efficacy was very limited so far. A recent research reported that NTCP c.800C > T mutation alone effected neither rosuvastatin concentrations nor the LDL-cholesterol reduction levels in Chinese hypercholesterolemia patients (Lee et al. 2013). However, they found an interaction between this mutation and OATP1B1 c.521T > C variant that patients with the combined genotype exhibited a relatively higher rosuvastatin concentrations than the patients with just NTCP c.800C > T mutation (Lee et al. 2013). Therefore, it would be more valuable to examine the cooperation effect of NTCP c.800C > T with OATP c.521T > C or/and BCRP c.421C > A polymorphisms on rosuvastatin pharmacokinetics and therapeutic efficacy. Another concern related to statin therapy is statin-induced myopathy, specifically for those with a long time usage. The mechanism underlying the statin-induced myopathy remains unclear, however, it is believed the elevated systemic exposure to statins is tightly associated with the higher incidence of statin-induced myopathy (Ghatak et al. 2010). A GWAS study by Link et al. (2008) demonstrated that the patients with OATP1B1c.521CC genotype had a higher risk of simvastatin-induced myopathy when using a high daily dose of 80 mg. This finding agreed well with the previous observation that markedly enhanced exposure to simvastatin acid were detected in the subjects with OATP1B1c.521CC variant genotype (Pasanen et al. 2006). Thereby, FDA recommended Asians who accepted rosuvastatin therapy begin at a very low dose (e.g. 5 mg) to avoid relevant adverse reactions based on the data from previous pharmacokinetic studies (Lee et al. 2005). Accordingly, in addition to OATP c.521T > C polymorphism, NTCP c.800C > T as well as BCRP c.421C > A variant could be presumed as candidate risk factors for rosuvastatin-induced myopathy. Further explorations are needed to confirm this presumption in large-size studies.

Besides rosuvastatin, some other statins such as fluvastatin atovastatin and pitavastatin were also identified as NTCP substrates (Ghatak et al. 2010; Choi et al. 2011). A *in vitro* study showed that fluvastatin was indeed a substrate of NTCP, but the low affinity ($K_m = 250\ \mu M$) implied a minor role of NTCP-mediate uptake at clinically relevant plasma concentration (Ghatak et al. 2010). However, NTCP c.800C > T SNP still had a profound impact on atovastatin uptake in the cellular assays (Choi et al. 2011), and the influence of this polymorphism on atovastatin pharmacokinetics in humans are unknown and need further studies.

To our knowledge, this is the first preliminary study to explore the relationship between NTCP c.800C > T polymorphism and rosuvastatin pharmacokinetics in healthy individuals. It was a shortcoming that our study was just carried out in a small numbers of subjects at a single oral dose of 10 mg rosuvastatin. In conclusion, NTCP c.800C > T polymorphism plays an important role in individual difference of rosuvastatin pharmacokinetics. Its genotype could be a new genetic marker, together with the OATP1B1 c.521T > C and BCRP c.421C > A variants, used to optimize the efficacy and toxicity of statin therapy via individualized selection of a dose for Asians.

4. Experimental

4.1. Subjects

305 unrelated Chinese healthy males were enrolled in this study. OATP1B1 c.521T > C (rs4149056, Val174Ala) and BCRP c.421C > A (rs2231142, Gln141Lys) were genotyped by pyro-sequencing method as described previously (Rohrbacher et al. 2006; Kim et al. 2010) and the genetic analysis of NTCP c.800C > T (rs2296651, Ser267Phe) were done by direct sequencing method using the following primers for PCR reaction, F: 5'CTCTGAGTGTATGTGGGGTTTTC 3'; R: 5' CCCTTGGGAGTCTTGAATTTCTC 3'. The sequencing analysis for these three polymorphisms are shown in Fig. 3. Finally, 17 healthy volunteers who were OATP1B1 c.521TT and BCRP c.421CC wild-type homozygotes with different NTCP genotype were recruited for the pharmacokinetic study. Nine were NTCP c.800CC wild-type homozygotes and eight subjects were with at least one c.800C > T variant allele (seven subjects with c.800CT genotype and one was c.800TT homozygote). Participants were 22 ± 3 years old, with a body mass index of $21.4 \pm 1.9\ kg/m^2$. All the subjects were ascertained to be healthy by medical history, physical examinations and routine laboratory tests before they signed the informed consents. No one was smoker or alcohol consumers and none was on any continuous medication in the recent three months. All subjects completed the entire protocol of this study.

4.2. Study design

The study protocol was approved by the Ethics Committee of Central South University (No.CTXY-110004-3). After an overnight fast, 17 subjects received a single oral dose of 10 mg rosuvstatin (one tablet; Crestor, AstraZeneca) with 150 mL warm water at 8:00AM. Two hours later subjects were allowed to drink. A standardized meal was supplied four hours after rosuvastatin administration. A series of 5 mL venous blood samples were collected into EDTA-containing tubes before and at 0.5,1,1.5,2,3,4,5,6,8,10,12,24,48,72 hours after rosuvastatin intake. Blood samples were centrifuged at 4 °C within half an hour and plasma was stored at −80 °C until the samples tested.

4.3. Determination of plasma rosuvastain concentration

The plasma concentration of rosuvastatin was measured by liquid chromatography–mass spectrometry with employing the Finnigan LCQ Deca XPplus (Finnigan, San Jose, CA) as described previously (Zhang et al. 2006). A Hypurity C18 column and a mobile phase consisting of methanol (80%) and 0.1% ammonium acid at a flow rate of 0.2 ml/min were applied.

Tramadol was chosen as the internal standard. The ion transitions monitored were as follows: m/z 482 to 464.1 and 446.2 for rosuvastatin and m/z 264 to 246 for tramadol. These transitions represent the product ions of the [M + H] + ions. The lower limit of quantification for rosuvastatin was 0.2 ng/ml. The assay range used was 0.2–50 ng/ml. Correlation coefficient for rosuvastatin calibration curves were 0.995. The highest rosuvastatin plasma concentration measured was 32.29 ng/ml.

4.4. Pharmacokinetic analysis

The area under the plasma concentration–time curve (AUC) of rosuvastatin were calculated by the linear trapezoidal rule; K_e is the slope of the linear terminal part of the plasma concentration vs. time curve after semilogarithmic transformation. The blood elimination half-life $T_{1/2} = 0.693/ K_e$ and $AUC_{(0\rightarrow\infty)} = AUC_{(0–72)} + C_{p(72\ h)}/K_e$ ($C_{p(72\ h)}$ is the plasma concentration at 72 h). The oral clearance (CL/*F*) was calculated as follows: CL/*F* = dose (10 mg)/$AUC_{(0–t)}$ (ng·h/ml). The maximum concentration (C_{max}) and the time to peak concentration (T_{max}) were directly determined from the plasma time–concentration curve.

4.5. Statistical analysis

Statistical analysis of data was done by the SPSS 13.0 software for windows (Chicago, IL, USA). Hardy–Weinberg equilibrium and allelic frequencies were compared using Pearson's χ^2 test. Normality tests were conducted on all pharmacokinetic parameters. Normally distributed data were analyzed by the Student's *t*-test, whereas non-normally distributed data were compared using the Mann–Whitney test. Data are expressed as mean ± standard deviation (SD) in the text and table and the figures. A P value < 0.05 was considered statistically significant.

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References

Carswell CI, Plosker GL, Jarvis B (2002) Rosuvastatin. Drugs 62: 2075–2085.

Chasman DI, Giulianini F, Macfadyen J, Barratt BJ, Nyberg F, Ridker PM (2012) Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) trial. Circ Cardiovasc Genet 5: 257–264.

Choi JH, Lee MG, Cho JY, Lee JE, Kim KH, Park K (2008) Influence of OATP1B1 genotype on the pharmacokinetics of rosuvastatin in Koreans. Clin Pharmacol Ther 83: 251–257.

Choi MK, Shin HJ, Choi YL, Deng JW, Shin JG, Song IS (2011) Differential effect of genetic variants of Na(+)-taurocholate co-transporting polypeptide (NTCP) and organic anion-transporting polypeptide 1B1 (OATP1B1) on the uptake of HMG-CoA reductase inhibitors. Xenobiotica 41: 24–34.

Craddock AL, Love MW, Daniel RW, Kirby LC, Walters HC, Wong MH, Dawson PA (1998) Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter. Am J Physiol Gastrointest Liver Physiol 274: G157-G169.

Ghatak A, Faheem O, Thompson PD (2010) The genetics of statin-induced myopathy. Atherosclerosis 210:337–343.

Greupink R, Dillen L, Monshouwer M, Huisman MT, Russel FG (2011) Interaction of fluvastatin with the liver-specific Na^+-dependent taurocholate cotransporting polypeptide (NTCP). Eur J Pharm Sci 44: 487–496.

Hagenbuch B, Meier PJ (1996) Sinusoidal (basolateral) bile salt uptake systems of hepatocytes. Semin Liver Dis 16:129–136.

Ho RH, Leake BF, Roberts RL, Lee W, Kim RB (2004) Ethnicity-dependent polymorphism in Na^+-taurocholate cotransporting polypeptide (SLC10A1) reveals a domain critical for bile acid substrate recognition. J Biol Chem 279: 7213–7222.

Ho RH, Tirona RG, Leake BF, Glaeser H, Lee W, Lemke CJ, Wang Y, Kim RB (2006). Drug and bile acid transporters in rosuvastatin hepatic uptake: function, expression, and pharmacogenetics. Gastroenterology 130: 1793–1806.

Huang L, Wang Y, Grimm S (2006) ATP-dependent transport of rosuvastatin in membrane vesicles expressing breast cancer resistance protein. Drug Metab Dispos 34: 738–742.

Keskitalo JE, Zolk O, Fromm MF, Kurkinen KJ, Neuvonen PJ, Niemi M (2009) ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 86: 197–203.

Kim KA, Joo HJ, Park JY (2010) ABCG2 polymorphisms, 34G > A and 421C > A in a Korean population: analysis and a comprehensive comparison with other populations. J Clin Pharm Thera 35: 705–712.

Lee E, Ryan S, Birmingham B, Zalikowski J, March R, Ambrose H, Moore R, Lee C, Chen Y, Schneck D (2005) Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 78: 330–341.

Lee HK, Hu M, Lui Sandra SH, Ho CS, Wong CK, Tomlinson B (2013) Effects of polymorphisms in ABCG2, SLCO1B1, SLC10A1 and CYP2C9/19 on plasma concentrations of rosuvastatin and lipid response in Chinese patients. Pharmacogenomics 14: 1283–1294.

Link E, Parish S, Armitage J, Bowman L, Health S, Matsude F, Gut I, Lathrop M, Collins R (2008) SLCO1B1 variants and statin-induced myopathy—a genome wide study. N Engl J Med 359: 789–799.

Pan W, Song IS, Shin HJ, Kim MH, Choi YL, Lim SJ, Kim WY, Lee SS, Shin JG (2011) Genetic polymorphisms in Na + /-taurocholate co-transporting polypeptide (NTCP) and ileal apical sodium-dependent bile acid transporter (ASBT) and ethnic comparisons of functional variants of NTCP among Asian populations. Xenobiotica 41: 501–510.

Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M (2006) SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics 16: 873–879.

Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M (2007) Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 82: 726–733.

Rohrbacher M, Kirchhof A, Skarke C, Geisslinger G, Lötsch J (2006) Rapid identification of three functionally relevant polymorphisms in the OATP1B1 transporter gene using Pyrosequencing. Pharmacogenomics 7: 167–176.

Romaine SP, Bailey KM, Hall AS, Balmforth AJ (2009) The influence of SLCO1B1 (OATP1B1) gene polymorphisms on response to statin therapy. Pharmacogenomics J 10: 1–11.

Tzeng TB, Schneck DW, Birmingham BK (2008) Population pharmacokinetics of rosuvastatin: implications of renal impairment, race, and dyslipidaemia. Curr Med Res Opin 24: 2575–2585.

Zamber CP, Lamba JK, Yasuda K, Farnum J, Thummel K, Schuetz EG (2003) Natural allelic variants of breast cancer resistance protein (BCRP) and their relationship to BCRP expression in human intestine. Pharmacogenetics 13: 19–28.

Zhang W, Yu BN, Yu, He YJ, Fan L, Li Q, Liu ZQ, Wang A, Liu YL, Tan ZR, Jiang F, Huang YF, Zhou HH (2006) Role of BCRP 421C > A polymorphism on rosuvastatin pharmacokinetics in healthy Chinese males. Clin Chim Acta 373: 99–103.