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Influence of the *CYP3A5* and *MDR1* genetic polymorphisms on the pharmacokinetics of tacrolimus in healthy Korean subjects

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What is already known about this subject

- It was found that the genetic polymorphisms of *CYP3A5, CYP3A4* and *MDR1* could affect the pharmacokinetics of tacrolimus.
- This study was conducted to find such a possibility in the Korean population.

What this study adds

- *CYP3A5* polymorphisms are likely to be associated with altered pharmacokinetics of tacrolimus in Koreans.
- *MDR1* polymorphisms have no important role in the pharmacokinetics of tacrolimus.

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Aims
To determine the frequencies of the genotypes of *CYP3A5* and *MDR1* and to examine the influence of the polymorphisms of these genes on tacrolimus pharmacokinetics in the Korean population.

Methods
Twenty-nine healthy Koreans who participated in the previous tacrolimus pharmacokinetic study were genotyped for *CYP3A4*1B*, *CYP3A5*3*, *MDR1* c.1236C→T, *MDR1* c.2677G→A/T and *MDR1* c.3435C→T. The relationship between the genotypes so obtained and tacrolimus pharmacokinetics observed in the previous study was examined.

Results
No subject in this study had the *CYP3A4*1B* variant. The observed frequencies of *CYP3A5*1/*1*, **1/*3*, and **3/*3* were 0.069 [confidence interval (CI) –0.023, 0.161], 0.483 (CI 0.301, 0.665) and 0.448 (CI 0.267, 0.629), respectively. $AUC_{0-\infty}$ for the *CYP3A5*1/*1* or **1/*3* genotype was 131.5 ± 44.8 ng h ml^{-1} (CI 109.6, 153.5), which was much lower compared with the *CYP3A5*3/*3* genotype of 323.8 ± 129.3 ng h ml^{-1} (CI 253.5, 394.1) (P = 2.063E–07). Similarly, C_{max} for the *CYP3A5*1/*1* or **1/*3* genotype was 11.8 ± 3.4 ng ml^{-1} (CI 10.1, 13.5), which was also much lower compared with the *CYP3A5*3/*3* genotype of 24.4 ± 12.3 ng ml^{-1} (CI 17.8, 31.1) (P = 0.0001). However, there was no significant difference in tacrolimus pharmacokinetics among the *MDR1* diplotypes of CGC-CGC, CGC-TTT, CGC-TGC, TTT-TGC or TTT-TTT (P = 0.2486).

Conclusions
This study shows that the *CYP3A5*3* genetic polymorphisms may be associated with the individual difference in tacrolimus pharmacokinetics. An individualized dosage regimen design incorporating such genetic information would help increase clinical efficacy of the drug while reducing adverse drug reactions.

Introduction

Tacrolimus, one of the calcineurin inhibitors, is highly effective in preventing acute rejection after transplantation of solid organs, including the liver and kidney [1]. However, tacrolimus shows high between- and within-subject variability in pharmacokinetics, with a narrow therapeutic index, necessitating therapeutic drug monitoring to optimize treatment [2–4].

It has become clear that the variability in the pharmacokinetics of tacrolimus is largely determined by differences in oral bioavailability [5]. Tacrolimus is a substrate of P-glycoprotein, the product of the multidrug resistance (*MDR1*) gene and has been known to undergo extensive hepatic metabolism by cytochrome P450 3A4 (CYP3A4) and CYP3A5 [6–8]. The variability in oral bioavailability of tacrolimus thus has been attributed to individual differences in expression of CYP3A4, CYP3A5 and P-glycoprotein [9].

A limited number of studies have reported on the association between *CYP3A4* variants and the pharmacokinetics of tacrolimus. Hesselink *et al*. found that *CYP3A4*1B* carriers require larger dose of tacrolimus to reach target trough concentrations compared with *CYP3A4*1* homozygotes [5]. In their work, it was established that the dose requirement for tacrolimus could be affected by *CYP3A5* variants. Several studies have reported that the dose-adjusted trough concentration of tacrolimus is much higher in *CYP3A5*3/*3* subjects than in **1/*1* or **1/*3* subjects [10–15]. The *CYP3A5*3* variant creates an alternative splice in pre-mRNA and produces aberrant mRNA that does not translate into functional CYP3A5 protein [16]. In contrast, numerous studies have investigated whether the genetic polymorphisms in *MDR1*, including c.1236C→T, c.2677G→A/T and c.3435C→T, could affect the pharmacokinetics of tacrolimus, yielding controversial results [9].

In a previous pharmacokinetic study, we compared the pharmacokinetics of twice-daily dosing of 1-mg tacrolimus capsules of two different formulations in healthy Korean volunteers: Prograf (Astellas Pharma Korea, Inc.), the reference, or conventional formulation, and TacroBell® (Chong Kun Dang Pharmaceutical Corp., Korea), the test, or newly developed formulation. While no significant difference in formulation was observed, we found high interindividual variability [51–76%, coefficient of variation (CV)] in the pharmacokinetics of tacrolimus and suspected a possible genetic polymorphism as a source of pharmacokinetic variation [17]. In this regard, this study was intended to see if such a possibility existed in the Korean population. Subjects who had participated in the previous tacrolimus pharmacokinetic study were therefore first examined for the frequencies of *CYP3A4*1B*, *CYP3A5*3* and three single nucleotide polymorphisms (SNPs) of *MDR1*, c.1236C→T, c.2677G→A/T and c.3435C→ T, and then for an association between the resulting genotypes and tacrolimus pharmacokinetics obtained in the previous study.

Materials and methods

Subjects

This study was approved by the institutional review board of Yonsei University Medical Centre, Seoul, Korea. A total of 29 unrelated healthy Korean volunteers participated in this study after giving written informed consent. They were recruited from the volunteers who had participated in the previous pharmacokinetic study of two oral formulations of tacrolimus [17].

Genetic analysis

We investigated the genotype frequencies of *CYP3A4*1B* (GenBank accession number AC069294), *CYP3A5*3* (GenBank accession number AC005020) and three SNPs of *MDR1*, c.1236C→T, c.2677G→A/T and c.3435C→T (GenBank accession numbers NC000007, NM000927) for the subjects by direct sequencing using an automated genetic analyser (Model 3700; Applied Biosystems, Foster City, CA, USA). The nomenclature of *CYP3A4* and *CYP3A5* was based on the website http://www.cypalleles.ki.se/. For each subject, one blood sample was collected and DNA was extracted using a purification kit (Qiagen, Hilden, Germany). Haplotype assembly was performed using the Haploview 3.2 program (Broad Institute of Harvard and MIT, Cambridge, MA, USA), based on a standard expectation-maximization algorithm to reconstruct individual haplotypes from population genotype data [18].

Pharmacokinetic data

For pharmacokinetic data, we used data obtained from the previous pharmacokinetic study, which can be summarized as follows [17]. It was as an open-label, randomized, two-period, cross-over study with a 3-week wash-out period in 29 healthy Korean volunteers. Each subject received two 1-mg capsules of a conventional (reference) or a newly developed (test) oral tacrolimus formulation twice a day, morning and evening (total daily dose of 4 mg). Blood samples were collected before dosing and at 0.5, 1, 1.5, 2, 3, 4, 7, 12, 12.5, 13, 13.5, 14, 15, 16, 19, 24, 36, 48, 72 and 96 h after dosing. Whole blood concentrations were analysed by LC/MS/MS. Pharmacokinetic parameters such as area under the concentration curve from time zero to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to C_{max} (t_{max}) and

half-life ($t_{1/2}$) for tacrolimus were estimated by noncompartmental analysis using WinNonlin Professional 4.1. In results, the two formulations were not significantly different and showed similarly large interindividual variation in tacrolimus pharmacokinetics [59.3–61.1% (test) and 50.7–75.6% (reference) in CV]. Therefore, in this study, without loss of generality, only the conventional formulation's pharmacokinetic data were used in examining genetic influences on tacrolimus pharmacokinetics.

Statistical analysis

Differences in pharmacokinetic parameters between the genotype groups were tested using the Wilcoxon rank sum test or the Kruskal–Wallis test. The frequency of *CYP3A5*3/*3* genotype was compared with that of the other ethnic groups, using χ^2 test. *P*-values < 0.05 were considered to be statistically significant.

Results

Polymorphisms of CYP3A5 *and* MDR1 *in Koreans*

Table 1 shows frequency distributions of *CYP3A5* and *MDR1* genotypes in 29 Korean subjects examined in this study. Each genotype did not deviate from Hardy–Weinberg equilibrium. Among the *CYP3A4*1B*, *CYP3A5*3* and *MDR1* genotypes examined in our study, the *CYP3A4*1B* genotype was not observed in any subject and the *CYP3A5*1/*1* genotype was observed in only two subjects, yielding a frequency of 0.069 [confidence interval (CI) –0.023, 0.161), with CI indicating a 95% CI. In contrast, for the *CYP3A5*3* variant, the heterozygous allele was observed in 14 subjects with a frequency of 0.483 (CI 0.301, 0.665), while the homozygous allele was observed in 13 subjects with a frequency of 0.448 (CI 0.267, 0.629). The frequency of *CYP3A5*3/*3* observed with our subjects was similar to that of 0.400 (CI 0.268, 0.532) with Chinese ($P = 0.5313$) or 0.583 (CI 0.512, 0.654) with Japanese ($P = 0.1737$) [19, 20]. However, some significant differences were also found in the frequency of this genotype. That is, the frequency of *CYP3A5*3/*3* genotype was higher in Koreans compared with the frequency of 0.029 (CI –0.027, 0.085) in African-Americans ($P = 0.0001$), but was much lower compared with the frequency of 0.830 (CI 0.756, 0.904) in Whites ($P = 0.0001$) [21, 22]. These results suggest that the frequency of *CYP3A5*3/*3* genotype is dependent on ethnicity.

The *MDR1* haplotypes were estimated from the three *MDR1* genotypes at c.1236C→T, c.2677G→A/T and c.3435C→T using a standard expectation-maximization algorithm (Table 2). Three major haplotypes that were relatively commonly observed were TTT, CGC and TGC, accounting for 41.4%, 20.7% and 20.7% of the total haplotype diversity, respectively. The combinations of these three predominant haplotypes constituted the five diplotypes examined in this study, CGC-CGC (3.4%, $n = 1$), CGC-TTT (17.2%, $n = 5$), CGC-TGC (10.3%, $n = 3$), TTT-TGC (31.0%, $n = 9$) and TTT-TTT (10.3%, $n = 3$) (Table 3).

Pharmacokinetic parameters of tacrolimus

In this study, pharmacokinetic values were given as mean ± SD with 95% CI. Table 4 shows that $AUC_{0-\infty}$ for the subject with the *CYP3A5*1/*1* or **1/*3* genotype

Table 1
Genotype frequencies for *CYP3A5* and *MDR1* in healthy Koreans ($n = 29$)

Variant	Genotype	No. (frequency)	95% CI
*CYP3A5*3*	*1/*1	2 (0.069)	(–0.023, 0.161)
	*1/*3	14 (0.483)	(0.301, 0.665)
	*3/*3	13 (0.448)	(0.267, 0.629)
MDR1 c.1236C→T	CC	3 (0.103)	(–0.008, 0.214)
	CT	12 (0.414)	(0.235, 0.593)
	TT	14 (0.483)	(0.301, 0.665)
MDR1 c.2677G→A/T	GG	4 (0.138)	(0.012, 0.264)
	GA	2 (0.069)	(–0.023, 0.161)
	GT	15 (0.517)	(0.335, 0.699)
	AT	1 (0.034)	(–0.032, 0.100)
	AA	2 (0.069)	(–0.023, 0.161)
	TT	5 (0.172)	(0.035, 0.309)
MDR1 c.3435C→T	CC	8 (0.276)	(0.113, 0.439)
	CT	17 (0.586)	(0.407, 0.765)
	TT	4 (0.138)	(0.012, 0.264)

Table 2
Haplotype frequencies of *MDR1* c.1236C→T, c.2677G→A/T, c.3435C→T in healthy Koreans ($n = 29$)

Haplotype	c.1236C→T	c.2677G→A/T	c.3435C→T	Frequency (95% CI)
TTT	T	T	T	0.414 (0.287, 0.541)
CGC	C	G	C	0.207 (0.103, 0.311)
TGC	T	G	C	0.207 (0.103, 0.311)
CAC	C	A	C	0.069 (0.004, 0.134)
TAC	T	A	C	0.034 (–0.013, 0.081)
TTC	T	T	C	0.034 (–0.013, 0.081)
CGT	C	G	T	0.017 (–0.016, 0.050)

Table 3
Tacrolimus pharmacokinetic parameters against major *MDR1* genotypes in healthy Koreans ($n = 21$)

Diplotype (no.)	$AUC_{0-\infty}$ (ng h ml^{-1})	C_{max} (ng ml^{-1})	t_{max} (h)	$t_{1/2}$ (h)
CGC-CGC (1)	565.7	30.9	2.0	31.2
CGC-TTT (5)	138.1 ± 38.9 (104.0, 172.2)	11.7 ± 3.5 (8.6, 14.8)	1.2 ± 0.3 (1.0, 1.4)	23.3 ± 12.6 (12.3, 34.4)
CGC-TGC (3)	233.0 ± 106.0 (113.1, 353.0)	18.3 ± 4.4 (13.3, 23.3)	1.7 ± 0.3 (1.3, 2.0)	23.4 ± 3.1 (19.9, 26.9)
TTT-TGC (9)	250.9 ± 157.8 (147.9, 354.0)	19.0 ± 13.4 (10.3, 27.7)	1.6 ± 0.9 (1.0, 2.2)	31.6 ± 12.0 (23.8, 39.4)
TTT-TTT (3)	200.3 ± 69.2 (122.0, 278.6)	16.3 ± 5.6 (9.9, 22.6)	1.3 ± 0.3 (1.0, 1.7)	33.9 ± 11.4 (21.0, 46.9)
P-value*	0.2486	0.3926	0.4733	0.4609

*Values are given as mean ± SD. Values in parentheses represent the 95% confidence interval. *Kruskal–Wallis test.*

Table 4
Tacrolimus pharmacokinetic parameters *vs. CYP3A5* genotypes in healthy Koreans ($n = 29$)

Genotype	$AUC_{0-\infty}$ (ng h ml^{-1})	C_{max} (ng ml^{-1})	t_{max} (h)	$t_{1/2}$ (h)
*CYP3A5 *1/*1* or **1/*3*	131.5 ± 44.8 (109.6, 153.5)	11.8 ± 3.4 (10.1, 13.5)	1.4 ± 0.7 (1.1, 1.7)	23.9 ± 11.9 (18.0, 29.7)
*CYP3A5 *3/*3*	323.8 ± 129.3 (253.5, 394.1)	24.4 ± 12.3 (17.8, 31.1)	1.6 ± 0.4 (1.4, 1.8)	30.6 ± 8.7 (25.9, 35.3)
P-value*	2.0630E–07	0.0001	0.1160	0.1103

*Values are given as mean ± SD. Values in parentheses represent the 95% confidence interval. *Wilcoxon rank sum test.*

was 131.5 ± 44.8 ng h ml^{-1} (CI 109.6, 153.5), which was much lower compared with the *CYP3A5*3/*3* genotype of 323.8 ± 129.3 ng h ml^{-1} (CI 253.5, 394.1) ($P = 2.063E{-}07$). Table 4 also shows that C_{max} for the subject with the *CYP3A5*1/*1* or **1/*3* genotype was 11.8 ± 3.4 ng ml^{-1} (CI 10.1, 13.5), which was also much lower compared with the *CYP3A5*3/*3* genotype of 24.4 ± 12.3 ng ml^{-1} (CI 17.8, 31.1) ($P = 0.0001$). The

values of t_{max} and $t_{1/2}$ were similar between the two genotype groups ($P = 0.1160$, 0.1103, respectively). The genotype differences in $AUC_{0-\infty}$ and C_{max} of tacrolimus are visually depicted in Figure 1.

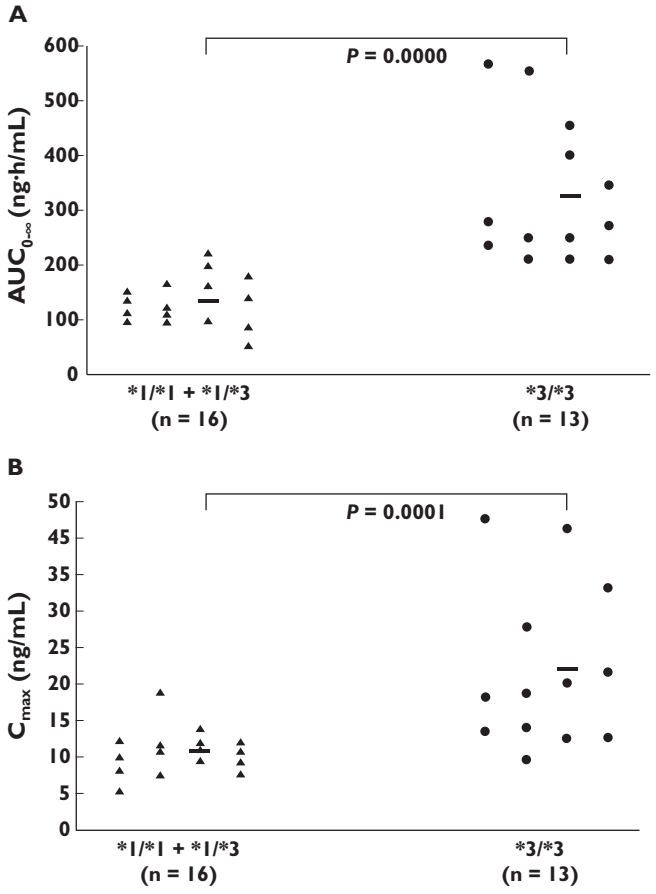

Figure 1
$AUC_{0-\infty}$ (A) and C_{max} (B) of tacrolimus illustrated according to the *CYP3A5* genotype. Triangles, *CYP3A5*1/*1* or **1/*3* ($n = 16$); circles, *CYP3A5*3/*3* ($n = 13$). A thick bar indicates the mean value of the group

There was no significant difference in pharmacokinetics of tacrolimus among the five *MDR1* diplotype groups ($P = 0.2486$) (Table 3).

Discussion

In the present study, we observed a significant association between the blood concentration of tacrolimus and the *CYP3A5*3* variant. Our results show that subjects with the *CYP3A5*1/*1* or **1/*3* genotype yield much lower $AUC_{0-\infty}$ and C_{max} values than the *CYP3A5*3/*3* genotype. To investigate other possibilities that may contribute to such pharmacokinetic differences, demographic factors including age, sex, height and body weight were compared between the two genotype groups. No demographic factor showed a significant difference between the two groups other than age, which showed distributions (mean ± SD) of 31.4 ± 8.3 years for the *CYP3A5*1/*1* or **1/*3* genotype *vs.* 25.6 ± 2.1 years for the *CYP3A5*3/*3* genotype ($P = 0.0153$) (Table 5). However, it has been reported that CYP3A activity is not significantly influenced by age [23].

Several studies have reported the interethnic variation in the pharmacokinetics of tacrolimus [24, 25]. In relation to interethnic differences in the frequency of the *CYP3A5*3* allele, Thompson *et al.* found that the frequency is lowest in sub-Saharan Africa and highest in European and East Asian populations, showing an increasing trend with distance from the equator [26]. Similarly in this work, we found that the *CYP3A5*3/*3* genotype was more common in Koreans and Whites than in African-Americans. The interethnic difference in the frequency of *CYP3A5*3/*3* genotype may contribute to the interethnic variation in the pharmacokinetics of tacrolimus.

In our subjects, no one had the *CYP3A4*1B* variant. According to the work by Lamba *et al.*, this genotype was not found in Japanese-Americans or in Chinese-

Table 5
Demographic characteristics of the *CYP3A5* genotype in healthy Koreans ($n = 29$)

Genotype	Sex (male:female)	Age* (years)	Weight* (kg)	Height* (cm)
*CYP3A5 *1/*1* or **1/*3*	12 : 4	31.4 ± 8.3 (20–51)	64.4 ± 9.0 (48–78)	170.5 ± 5.4 (160–182)
*CYP3A5 *3/*3*	10 : 3	25.6 ± 2.1 (23–30)	68.7 ± 11.1 (48–87)	172.2 ± 8.5 (155–181)
P-value	>0.9999†	0.0153‡	0.2760‡	0.5314‡

**Values are given as mean ± SD. Values in parentheses represent the range. †Fisher's exact test. ‡t-test.*

Americans, while frequencies of 2.0–9.6% and 35–67% were observed in Whites and African-Americans, respectively [16]. These findings indicate that the frequency of the *CYP3A4*1B* allele may vary among ethnic groups.

In our results, no significant difference was found in tacrolimus pharmacokinetics against *MDR1* polymorphisms in c.1236C→T, c.2677G→A/T or c.3435C→T, indicating a nonsignificant association between the blood concentration of tacrolimus and these three genotype groups (data not shown). Although many researchers have tried to examine whether these three SNPs could affect the expression and function of MDR1, the results are still controversial [27]. Recently, it has been confirmed that *MDR1* c.3435C→T is in significant linkage disequilibrium with c.1236C→T and c.2677G→A/T and the analysis of *MDR1* haplotypes may be superior to that of SNPs in revealing genotype–phenotype associations in pharmacokinetic studies [8, 27–29].

In our work, we estimated the *MDR1* haplotypes from the three *MDR1* genotypes at c.1236C→T, c.2677G→A/T and c.3435C→T using a standard expectation-maximization algorithm. Three predominant haplotypes were observed and the combinations of these three haplotypes constituted the five diplotypes, with no significant difference observed in tacrolimus pharmacokinetics among these five *MDR1* diplotypes. Thus, although it was found that the subject with CGC-CGC diplotype showed much higher $AUC_{0-\infty}$ and C_{max} compared with the other subjects (Table 3), this may be mainly due to the influence of the *CYP3A5*3/*3* genotype of this subject (Table 4).

In conclusion, our study demonstrates that the *CYP3A5* genetic polymorphisms may be associated with the pharmacokinetic variation of tacrolimus in Korean populations. Therefore, dosage regimen design incorporating genetic polymorphisms in *CYP3A5* may be of help in identifying the optimal dose for the individual patient.

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