DOI:10.1111/j.1365-2125.2006.02733.x



# Effect of *ABCB1* (*MDR1*) haplotypes derived from G2677T/C3435T on the pharmacokinetics of amlodipine in healthy subjects

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**Keywords**
*ABCB1* (*MDR1*), amlodipine , P-glycoprotein, pharmacogenetics, pharmacokinetics, polymorphism

**Received**
5 October 2005
**Accepted**
19 April 2006
**Published** *OnlineEarly*
21 July 2006

**Aim**
We aimed to investigate the effect of the *ABCB1* gene on the pharmacokinetics of amlodipine.

**Methods**
Based on polymorphisms of the *ABCB1* gene at positions 2677 and 3435, 26 healthy male participants were divided into three groups: subjects with 2677GG/3435CC ($n$ = 9), 2677GT/3435CT ($n$ = 9) and 2677TT/3435TT ($n$ = 8). After a single-dose administration of 5 mg amlodipine, plasma concentrations of amlodipine were measured and its pharmacokinetic characteristics were compared according to *ABCB1* genotype.

**Results**
The area under the plasma concentration–time curve was significantly lower in subjects with 2677TT/3435TT (140.8 ± 35.6 ng $h^{-1}$ $ml^{-1}$) and 2677GT/3435CT (149.8 ± 40.1 ng $h^{-1}$ $ml^{-1}$) than in those with 2677GG/3435CC (208.6 ± 39.2 ng $h^{-1}$ $ml^{-1}$) [95% confidence interval (CI) on the difference, 2677GG/3435CC *vs.* 2677GT/3435CT 12.0, 105.6, $P < 0.01$; 2677GG/3435CC *vs.* 2677TT/3435TT 19.6, 116.0, $P < 0.01$; 2677GT/3435CT *vs.* 2677TT/3435TT −39.2, 57.2, $P > 0.05$]. The peak plasma concentrations were highest in subjects with 2677GG/3435CC (3.8 ± 0.5 ng $ml^{-1}$), lower in subjects with 2677GT/3435CT (3.2 ± 0.5 ng $ml^{-1}$) and 2677TT/3435TT (2.7 ± 0.5 ng $ml^{-1}$) in rank and showed a significant difference between those with 2677GG/3435CC and with 2677TT/3435TT (95% CI on the difference 0.4, 2.0, $P < 0.01$). However, the oral clearance was higher in subjects with 2677TT/3435TT (37.7 ± 10.2 l $h^{-1}$) than in those with 2677GT/3435CT (35.7 ± 9.9 l $h^{-1}$) and with 2677GG/3435CC (24.8 ± 5.4 l $h^{-1}$) and exhibited a significant difference between *ABCB1* genotype groups (95% CI on the difference, 2677GG/3435CC *vs.* 2677GT/3435CT −21.5, −0.3, $P < 0.05$; 2677GG/3435CC *vs.* 2677TT/3435TT −23.8, −2.0, $P < 0.05$).

**Conclusion**
Amlodipine pharmacokinetics was affected by the genetic polymorphisms of the *ABCB1* gene in humans. These findings may provide a plausible explanation for interindividual variation in the disposition of amlodipine, although our study could not explain the exact mechanism(s) by which the polymorphic *ABCB1* gene paradoxically reduces the plasma levels of amlodipine. Further evaluation is thus warranted.

## Introduction

The 170-kDa membrane protein P-glycoprotein (P-GP) is an adenosine triphosphate (ATP)-dependent drug efflux pump that is constitutively expressed in several human tissues [1, 2]. Recent pharmacogenomic studies have shown that differential expression of the *ABCB1 (MDR1)* gene can influence the activity and bioavailability of drugs [3].

Amlodipine, a third-generation dihydropyridine calcium channel blocker, is prescribed for the management of angina and hypertension [4–6]. Recent evidence suggests that amlodipine acts as a substrate of P-GP [7, 8]. Furthermore, grapefruit juice and diltiazem, known inhibitors of P-Gp [9–11], affect the pharmacokinetics of amlodipine [12, 13]. We can speculate that amlodipine acts as a substrate of P-GP, the activity of which thus influences the pharmacokinetic characteristics of amlodipine as a factor of interindividual variation.

We therefore investigated the effect of genetic polymorphisms of the *ABCB1* gene, especially at positions 2677 and 3435, on the pharmacokinetics of amlodipine in healthy subjects.

## Materials and methods

### *Subjects*

Among the previously genotyped 160 subjects for *ABCB1* exons, exon 21 G2677T/A and exon 26 C3435T polymorphisms, we enrolled 26 men into this study: nine with 3435CC/2677GG (mean age ± SD 24.7 ± 2.2 years; mean weight ± SD 67.8 ± 7.1 kg), nine with 3435CT/2677GT (mean age ± SD 24.7 ± 2.2 years; mean weight ± SD 70.7 ± 5.4 kg) and eight with 3435TT/2677TT (mean age ± SD 26.9 ± 2.6 years; mean weight ± SD 68.9 ± 4.5 kg). The study protocol was approved by the Institutional Review Board (IRB) of Gil Medical Centre, Incheon, Korea and all subjects provided written informed consent.

### *Study procedures*

All subjects were admitted to the clinical trial centre the evening before the day of drug administration. The following morning, they were given a single oral dose of 5 mg amlodipine. Blood samples were collected immediately prior to drug administration and then at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48, 96 and 144 h after drug administration.

### *Genotyping of ABCB1 polymorphism*

DNA was extracted from peripheral whole blood of each subject using a Qiagen DNA extraction kit (Qiagen, Hilden, Germany). The genotypes of *ABCB1,* G2677T, G2677A and C3435T were identified by polymerase chain reaction-restriction fragment length polymorphism analysis as described previously [14–16] and results were confirmed for randomly selected individuals for each genotype by direct sequence analysis.

### *Drug analysis and pharmacokinetic analysis*

Plasma amlodipine concentrations were analysed using validated high-performance liquid chromatography with fluorescence detection as described previously with a slight modification [17]. A linearity calibration curve in the range of 0.1–10 ng ml$^{-1}$ was established for amlodipine ($r^2 = 0.9997$). Intraday and interday coefficients of variation (CV) were <8% and <10%, respectively,

The software WinNONLIN professional version 4.1 (Pharsight Corp. Inc., Mountain View, CA, USA) was used for pharmacokinetic analysis and simulations. The peak plasma concentration ($C_{max}$) and the time to reach $C_{max}$ ($t_{max}$) were estimated directly from the observed plasma concentration–time data. The area under the plasma concentration–time curve from time 0–144 h ($AUC_{last}$) was calculated using the linear trapezoidal rule. The AUC from time 0 to infinity ($AUC_{inf}$) was calculated as $AUC_{inf} = AUC_{last} + C_t/k_e$, where $C_t$ is the last plasma concentration measured and $k_e$ is the elimination rate constant; $k_e$ was determined using linear regression analysis of the logarithm-linear part of the plasma concentration–time curve. The half-life ($t_{1/2}$) of amlodipine was calculated as $t_{1/2} = \ln 2/k_e$. The oral clearance (CL/F) of amlodipine was calculated as $CL/F = dose/AUC_{inf}$.

### *Statistical analysis*

Statistical comparisons among *ABCB1* genotypes were made with one-way ANOVA, followed by *a posteriori* testing with the Bonferroni test. Statistical analyses were performed using the statistical software package Sigmastat for Windows (version 3.1; Systat Software Inc., Richmond, CA, USA). A *P*-value ≤0.05 was considered to be significant.

## Results

The plasma concentration–time profiles of amlodipine were compared among subjects with different *ABCB1* genotypes after a single-dose administration of 5 mg amlodipine and it was found that the plasma concentrations in subjects with 2677GT/3435CT and 2677TT/3435TT were lower than in those with 2677GG/3435CC (Figure 1). In addition, the average values of $AUC_{inf}$ were highest in subjects with 2677GG/3435CC (208.6 ± 39.2 ng h$^{-1}$ ml$^{-1}$) and lower in subjects with 2677GT/3435CT (149.8 ± 40.1 ng*h/ml) and 2677TT/3435TT (140.8 ± 35.6 ng h$^{-1}$ ml$^{-1}$) in rank with statisti-

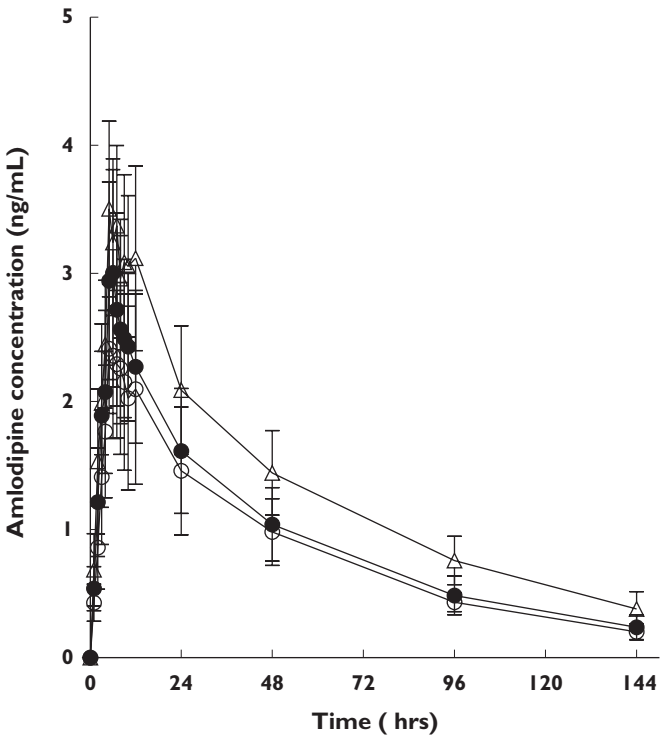


**Figure 1**

Plasma concentration–time curve of amlodipine after administration of 5 mg amlodipine orally according to *ABCB1* genetic polymorphisms at positions of G2677T and C3435T. Values are given as mean ± SD. 2677GG/3435CC (△); 2677GT/3435CT (●); 2677TT/3435TT (○)

cal significance [95% confidence interval (CI) on the difference, 2677GG/3435CC *vs.* 2677GT/3435CT 12.0, 105.6, $P < 0.01$; 2677GG/3435CC *vs.* 2677TT/3435TT 19.6, 116.0, $P < 0.01$; 2677GT/3435CT *vs.* 2677TT/3435TT −39.2, 57.2, $P > 0.05$] (Table 1). In addition, subjects with 2677GG/3435CC showed a significant difference in $C_{max}$ values from those with 2677TT/3435TT [95% CI on the difference ($l\,h^{-1}$) 0.4, 2.0, $P < 0.01$]. However, oral clearance of amlodipine was lower in subjects with 2677GG/3435CC than in those with 2677GT/3435CT [95% CI on the difference (ng $ml^{-1}$) 0.4, 2.0, $P < 0.01$] and 2677TT/3435TT [95% CI on the difference (ng $ml^{-1}$) 0.4, 2.0, $P < 0.01$] by 44% and 52%, respectively ($P = 0.01$) (Table 1). Pharmacokinetic parameters of amlodipine according to *ABCB1* genotypes are summarized in Table 1.

## Discussion

The results of the present study suggest that polymorphisms of the *ABCB1* gene affect the disposition of amlodipine in humans. Subjects with mutant alleles (2677TT/3435TT) of the *ABCB1* gene, especially, showed an increase in the oral clearance of amlodipine with its lower plasma concentrations compared with those with heterozygote (2677GT/3435CT) or wild type (2677GG/3435CC). We first hypothesized that if P-GP plays a crucial role in the disposition of amlodipine, subjects with polymorphic *ABCB1* gene might show higher plasma concentrations of amlodipine compared with those with wild-type allele. On the supposition that amlodipine is a substrate of P-GP [7, 8] and that coadministration of grapefruit juice [9] or diltiazem [11], known inhibitors of P-GP, increased the concentrations of amlodipine in humans [12, 13], polymorphisms of the *ABCB1* gene would cause increases in the plasma concentrations of amlodipine. However, on the contrary, subjects with the mutant *ABCB1* gene showed a decrease in plasma concentrations of amlodipine and an increase in the oral clearance in this study. AUC values were 33% lower in subjects with 2677GG/3435CC and 28% lower in those with 2677GT/3435CT compared with those with 2677TT/3435TT. Despite the belief that the polymorphic *ABCB1* gene should be an important determinant of interindividual variations in the disposition of amlodipine, contrary to our results, no association [18] or higher concentrations of other P-GP substrates in 2677TT/3435TT compared with 2677GG/3435CC have been reported in other studies [19, 20].

Unfortunately, we do not fully understand the mechanism(s) of why the polymorphic *ABCB1* gene paradoxically reduced the plasma concentrations of amlodipine in this study. Gender differences and interethnic differences in *ABCB1* haplotypes have generally been suggested to explain the discrepancies in the findings [21]. However, we could rule out the potential role of gender difference because only male subjects were enrolled in this study. Regarding the ethnic difference in *ABCB1* genotype, different patterns of linkage disequilibrium are found in different population groups [22, 23]. Therefore, a significant but unidentified single nucleotide polymorphism (SNP) might cause inconsistent results. In the current study, we recruited only the most frequently observed haplotypes in a Korean population. Among 160 subjects screened for SNPs of the *ABCB1* gene in this study, major haplotypes 2677G/3435C, 2677G/3435T and 2677T/3435T constituted 42.5%, 13.8% and 28.1% of all haplotypes, respectively, adding up to a total of 84.4%, and the genotype frequencies observed in this study are similar to previous observations in Asian populations [22, 23]. However, remarkable ethnic differences in the frequencies of SNPs of the *ABCB1* gene have been reported [24, 25]. Recently it has been reported that the combination of certain SNP variants into haplotypes might be of higher value in

**Table 1**
Pharmacokinetic profiles of amlodipine after administration of a single dose of 5 mg amlodipine according to the genetic polymorphisms of the *ABCB1* gene at positions 2677 and 3435

| | | | | Difference between genotypes | | | |
|---|---|---|---|---|---|---|---|
| Parameter | 2677GG/3435CC | 2677GT/3435CT | 2677TT/3435TT | 2677GG/3435CC & 2677GT/3435CT | 2677GG/3435CC & 2677TT/3435TT | 2677GT/3435CT & 2677TT/3435TT | *P*-value |
| $C_{max}$ (ng ml$^{-1}$) | 3.8 ± 0.5 | 3.2 ± 0.5 | 2.7 ± 0.5 | 0.6 | 1.2† | 0.5 | 0.006 |
| (95% CI) | (3.5, 4.1) | (2.6, 3.8) | (2.3, 3.1) | (–0.2, 1.4) | (0.4, 2.0) | (–0.3, 1.3) | |
| $t_{max}$ (h) | 5 | 6 | 6 | 0.9 | –0.3 | –1.2 | 0.828 |
| (range) | (5.0–12.0) | (5.0–8.0) | (5.0–12.0) | (–1.7, 3.5) | (–3.0, 2.4) | (–3.9, 1.5) | |
| Half-life (h) | 51.8 ± 10.9 | 46.3 ± 7.1 | 43.0 ± 5.6 | 5.5 | 8.8 | 3.3 | 0.132 |
| (95% CI) | (44.7, 58.9) | (41.7, 50.9) | (39.1, 46.9) | (–4.6, 15.6) | (–1.6, 19.2) | (–7.1, 13.7) | |
| $AUC_{last}$ (ng h$^{-1}$ ml$^{-1}$) | 180.9 ± 29.0 | 133.6 ± 33.1 | 125.1 ± 33.0 | 47.3* | 55.9† | 8.5 | 0.003 |
| (95% CI) | (161.9, 199.9) | (111.9, 155.3) | (102.2, 148.0) | (8.7, 85.9) | (16.1, 95.7) | (–31.3, 48.3) | |
| $AUC_{inf}$ (ng h$^{-1}$ ml$^{-1}$) | 208.6 ± 39.2 | 149.8 ± 40.1 | 140.8 ± 35.6 | 58.8† | 67.8† | 9.0 | 0.002 |
| (95% CI) | (183.0, 234.2) | (123.6, 176.0) | (116.1, 165.5) | (12.0, 105.6) | (19.6, 116.0) | (–39.2, 57.2) | |
| CL/F (l h$^{-1}$) | 24.8 ± 5.4 | 35.7 ± 9.9 | 37.7 ± 10.2 | –10.9* | –12.9* | –2.1 | 0.010 |
| (95% CI) | (21.3, 28.3) | (29.2, 42.2) | (30.6, 44.8) | (–21.5, –0.3) | (–23.8, –2.0) | (–13.0, 8.8) | |

*Data are shown as mean ± SD.* $t_{max}$ *is given as median (range).* $C_{max}$, *Peak plasma concentration;* $t_{max}$, *time to* $C_{max}$; $AUC_{last}$, *area under the time–concentration curve from 0 to 144 h;* $AUC_{inf}$, *area under the time–concentration curve from 0 to infinity; CL/F, oral clearance.* *P < *0.05 by* ANOVA *with Bonferroni correction* a posteriori *for wild-type group;* †P < *0.01 by* ANOVA *with Bonferroni correction* a posteriori *for wild-type group.*

predicting P-GP activity [19]. The authors demonstrated that there are significant differences in the pharmacokinetics of digoxin, a substrate of P-GP, between carriers and noncarriers of haplotypes between G2677T and C3435T. Therefore, we recruited subjects with simultaneous wild, heterozygous, or mutant types of the *MDR1* gene at positions 2677 and 3435. Even though our findings showed apparent discrepancies with the previous findings [18–20], our observations are similar to the results of studies using fexofenadine or digoxin as a substrate of P-GP, which showed that subjects with 2677GG/3435CC showed a lower concentration of P-GP substrate than those with 2677TT/3435GG [26–28]. Therefore, haplotype analysis rather than analysis of each genotype may be more crucial in determining the pharmacokinetic characteristics of amlodipine.

In conclusion, amlodipine pharmacokinetics was affected by the polymorphic *ABCB1* gene in humans. These findings may provide a plausible explanation for interindividual variation in the disposition of amlodipine, although our study could not explain the exact mechanism(s) of why polymorphic *ABCB1* gene paradoxically reduces the plasma levels of amlodipine; this warrants further evaluation.

*This study was supported by a grant of the Korea Health 21 R&D Project. Ministry of Health & Welfare, R. O. K. (03-PJ10-PG13-GD01-0002).*

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