Regular Article

ABCB1 Polymorphism and Gender Affect the Pharmacokinetics of Amlodipine in Chinese Patients with Essential Hypertension: A Population Analysis

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Summary: The effects of genetic polymorphisms of ABCB1 C3435T, POR*28, CYP3A4*1G and CYP3A5*3 variants and gender relating to metabolism on the exposure and response of amlodipine in Chinese hypertensive patients were determined. Population pharmacokinetic analyses were performed on data which were collected prospectively from 60 Chinese patients with mild to moderate essential hypertension [age range 40–74 years, males (n = 31), females (n = 29)] receiving oral racemic amlodipine for 4 weeks. Blood pressure was evaluated at the end of weeks 0 and 4. Blood samples were collected in heparinized tubes at the following times: 0, 2, 6, and 24 h on about day 28 after administration of amlodipine. A one-compartment model with first-order elimination and absorption best described the amlodipine pharmacokinetic data. ABCB1 3435 genetic polymorphism and gender affect the amlodipine oral clearance (CL/F). CL/F (L/h) = 28.8 × (1 + GNDR)^-0.531 × (ABCB1 C3435T) where GNDR = 0 and 1 are for male and female, respectively. The CL/F value in a male patient with the ABCB1 3435CC or CT genotype is 28.8 L/h. Lower CL/F and higher exposure occurs in female subjects with the ABCB1 3435CC or CT genotype who have greater decreases in blood pressure after treatment with amlodipine. The results may help to improve the efficacy and tolerability of amlodipine in essential hypertensive patients.

Keywords: ABCB1 C3435T; gender; amlodipine; hypertension; population pharmacokinetics

Introduction

Amlodipine, a third-generation calcium antagonist, is mainly used in the treatment of angina and hypertension diseases.1 It has been shown to suppress the calcium influx through the L-type calcium channel in peripheral vascular and coronary smooth muscle cells, thus leading to significant vasodilation in peripheral and coronary vascular beds. Structural characteristics of amlodipine offer unique pharmacokinetic properties among calcium antagonists. It has a relatively high bioavailability, ranging from 65% to 90%, and higher tissue affinity, which resulted in a relatively long time to peak plasma concentration (Cmax) of 6–12 h and a longer plasma elimination half-life (t1/2) of 30–50 h compared with other dihydropyridine calcium antagonists.

What’s more, 90% of an amlodipine oral dose is converted to inactive metabolites in the liver. Amlodipine functions as a substrate of cytochrome P450 (CYP) 3A42,3 and P-glycoprotein (P-gp), product of the multidrug resistance 1 (MDR1, known as the ABCB1) gene.4,5 In studies of healthy subjects, our previous study6 and Kim et al.7 showed that the CYP3A5*3 allele is a main
determinant of the apparent clearance (CL/F) of amlodipine. The polymorphic ABCB1 gene in humans may also explain the interindividual variation in the disposition of amlodipine. Among African-American men and women with early hypertensive renal disease, the CYP3A4 genotype appears to be associated with blood pressure response to amlodipine. Genetic and environmental factors contribute towards the variability of drug response. To determine the multifactorial effects on the exposure and response of amlodipine, we developed a population pharmacokinetic model of amlodipine in Chinese patients with mild to moderate essential hypertension and investigated the potential role of the CYP3A and ABCB1 genetic polymorphisms in the variability of amlodipine disposition through assessing pharmacokinetic parameters and the association of genotypes on the CYP3A and ABCB1 genes with blood pressure responses to amlodipine.

Materials and Methods

Patients: For all patients, informed consent in accordance with the guidelines of the declaration of Helsinki was obtained for the study, which had been approved by the Third Xiangya Hospital of Central South University Ethics Committee. The clinical trial included 60 Han Chinese men and women between the ages of 40 and 75 years and diagnosed with mild to moderate essential hypertension (mean seated systolic blood pressure (SBP) 140–180 mmHg or diastolic blood pressure (DBP) 90–110 mmHg), and taking stable doses of amlodipine. Subjects were excluded if they had a history of secondary hypertension, severe hypertension, acute phase of cerebral stroke, congestive heart failure, unstable angina pectoris, acute myocardial infarction within the previous 6 months, arrhythmia, bilateral renal artery stenosis, hyperkalemia, cancer, severe hepatic or renal diseases, or were unable to provide informed consent. Pregnant women, breastfeeding women, alcohol or drug addicts and those with mental disabilities were also not enrolled.

Study design: After eligibility was confirmed and consent obtained, patients were scheduled for the trial. The study consisted of two phases: a 1-week placebo washout phase and a 4-week treatment period with amlodipine 5 mg once daily.

Subjects with antihypertensive drugs had the medication discontinued just before entry into the placebo washout phase. Participants were entered into the treatment phase if their mean seated systolic blood pressure was between 140 and 180 mmHg or diastolic blood pressure was between 90 and 110 mmHg. They received amlodipine 5 mg once daily during the treatment phase. To ensure the patients’ compliance with amlodipine treatment, patients with good compliance were reminded to take their medicine every day by our appointed community physicians.

On day 1 of the placebo washout phase, the following evaluation was performed for patients to meet all inclusion criteria: complete medical history and routine physical exam, blood pressure and heart rate, 12-lead electrocardiograph (ECG), and clinical laboratory testing.

Patients were evaluated at the initiation and end of the washout day, and the end of the treatment study. Their visits were scheduled in the morning, and all evaluations were performed at drug trough level (24 ± 2 h after the previous day’s dose) and before the next dose was taken. The following evaluations were performed at the end of weeks 0 and 4: demographic data, blood pressure, heart rate, concomitant drugs, and other related clinical items.

Sampling: On about day 28, patients were admitted to the Research Center of Clinical Pharmacology for 24-h pharmacokinetic and pharmacodynamic assessments. Five ml blood samples were collected in heparinized tubes at the following times: 0, 2, 6, and 24 h after administration of amlodipine. Samples were centrifuged at 3,000 rpm for 10 min and the plasma was separated and stored at −20°C until analysis. Double tubes of each sample were kept.

Determination of amlodipine concentrations: Plasma amlodipine concentrations were analyzed by LC-MS/MS consisting of API 4000 triple-quadrupole tandem mass. Detection was performed by ESI+ in MRM mode. For details, see our published articles. The lower limit of quantification was 0.081 ng/ml and standard calibration curves showed good linearity within the range of 0.0810 ng/ml to 36.31 ng/ml (r² = 0.9956). The intra-day and inter-day coefficients of variation of all assays were less than 15%.

Genotyping: DNA was extracted from peripheral whole blood of each subject using a Promega DNA extraction kit (DNA Mini-Prep Kit, Promega, Madison, WI). The genotypes of ABCB1 C3435T (rs1045642), CYP3A4 G20230A (CYP3A4*1G, rs2242480) and CYP3A5 A6986G (CYP3A5*3, rs776746), and P450 oxidoreductase (POR) A503V (POR*28, rs1057868) were identified by polymerase chain reaction-restriction fragment length polymorphism analysis as described previously and results were confirmed for randomly selected individuals for each genotype by a developed and validated automated DNA sequencer (ABI PRISM 3730 Sequence Detection System; Applied Biosystems) in Shanghai Sangon Biological Engineering Technology & Services Co., Ltd. (Shanghai, China). Hardy-Weinberg equilibrium was assessed by using the Pearson goodness of fit (χ²) test.

Pharmacodynamics: Blood pressure determinations were made using the calibrated Electronic Blood Pressure Monitor (HEM-7012, Omron Co. Inc., Tokyo, Japan) and the patient’s same arm throughout the course of the study. Blood pressure taken on day 0 was recorded in both arms. Seated blood pressure was obtained on the sampling day at 0h.

Population pharmacokinetic model development: The data were graphically presented using R software, version 2.14.0 (R foundation for statistical computing, http://www.r-project.org). The nonlinear mixed-effects modeling software program NONMEM (version VII, level 2.0; ICON Development Solutions, Ellicott City, MD) was used to determine amlodipine’s population pharmacokinetic using first-order conditional estimation method with the subroutines ADVAN2 TRANS2. Maximum likelihood estimates were carried out for CL/F and apparent volume of distribution (V/F). Various compartmental models and combinations of interindividual and residual error models were assessed in describing the plasma concentration-time data for amlodipine.

Subject covariate analysis

Factors screened for effects on these parameters included the following: gender (GNDR), age, height, body weight, body mass index, history of smoking, drinking and family hypertension, POR, CYP3A4, CYP3A5 and ABCB1 genotypes, alanine aminotransferase, aspartate aminotransferase, total protein (TP), total bilirubin, direct bilirubin, blood urea nitrogen, serum creatinine, uric acid, hematocrit, and co-administration with drugs such as insulin, metformin, acarbose and aspirin.

Continuous covariates were plotted against each subject number to identify correlations between any two covariates. Box plots of continuous covariates, sorted by categorical covariates, were also created to identify the potential relationships between any two covariates. Covariates with visual relationships were separately
examined further by NONMEM for statistical significance. Those identified as potentially influencing pharmacokinetic parameters were then incorporated stepwise into the model.

Parameter-covariate relationships were included in a full tentative pharmacokinetic model if the covariate contributed at least a 3.84 change in the objective function ($\alpha = 0.05$ for 1 degree of freedom, $\chi^2$). Covariates were then excluded from the model using a simple backward elimination method if the covariate relationship did not contribute at least a 7.88 change in the objective function ($\alpha = 0.005$ for 1 degree of freedom, $\chi^2$).

**Model assessment and validation**

Graphic plots for validation of the population pharmacokinetic model were constructed as follows: population predicted (PRED) and individual predicted (IPRED) values versus observed concentrations (DV), and PRED versus conditional weighted residuals (CWRES). The accuracy and robustness of the final model selected was checked using the nonparametric bootstrap method and the standardized visual predictive check (SVPC) method. Internal validation was undertaken using bootstrapping with the Perl speaks NONMEM (PsN) program (version 3.5.3).

SVPC displays observations and predictions on a standardized scale. SVPC is better than VPC when there are multiple categorical covariate effects on pharmacokinetic parameters. The SVPC shows the percentile of each observation of each participant in the marginal distribution of model-simulated endpoints ($P_{i,j}$) as a function of time using that participant’s own design template. In this study, 1,000 data sets were simulated using the final model based on the original data set by setting NSUBPROBLEMS = 1,000 in NONMEM to implement the SVPC.

**Statistical analysis:** SPSS for Windows (version 18.0; SPSS Inc., Chicago, IL) was used to analyze data described as mean ± SD. The allele and genotype frequencies of the CYP3A and ABCB1 polymorphisms were assessed for deviation from the Hardy–Weinberg equilibrium using the $\chi^2$ test. Pearson’s product-moment correlation was used to examine the relationship between the area under the concentration–time curve (AUC) of amlodipine and the difference of seated systolic blood pressure from its baseline value. p values of less than 0.05 were considered statistically significant.

### Table 1. Demographic, biological, and genetic data for patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value*</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>60</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Number of amlodipine concentrations</td>
<td>228</td>
<td>120</td>
<td>108</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 (40, 74)</td>
<td>61 (40, 74)</td>
<td>58 (41, 71)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 (45, 100)</td>
<td>73.5 (52, 100)</td>
<td>62 (45, 77)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 (1.48, 1.71)</td>
<td>1.67 (1.59, 1.71)</td>
<td>1.57 (1.48, 1.71)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 (16.5, 34.6)</td>
<td>25.4 (19.7, 34.6)</td>
<td>24.6 (16.5, 29.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>151 (133, 177)</td>
<td>151 (133, 177)</td>
<td>151 (133, 171)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>91 (71, 107)</td>
<td>91 (72, 107)</td>
<td>91 (71, 105)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>130 (99, 167)</td>
<td>138 (99, 167)</td>
<td>125 (100, 150)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>23 (15, 64)</td>
<td>23 (18, 63)</td>
<td>25 (15, 64)</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>23.5 (7, 88)</td>
<td>26 (7, 88)</td>
<td>23 (8, 81)</td>
</tr>
<tr>
<td>Total bilirubin (mmol/L)</td>
<td>12.2 (5.0, 31.7)</td>
<td>12.0 (5.0, 31.7)</td>
<td>12.2 (5.5, 22.4)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>5.01 (2.28, 13.85)</td>
<td>5.06 (2.70, 13.85)</td>
<td>4.54 (2.28, 8.02)</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>69 (25, 330)</td>
<td>69 (25, 330)</td>
<td>56.5 (33, 148)</td>
</tr>
</tbody>
</table>

*Values are expressed as median (range) unless specified otherwise.

### Results

**Patient demographics:** Data were collected from 60 adult patients with mild to moderate essential hypertension (31 men, 29 women). Patient characteristics are presented in Table 1. All SNP distributions of the POR*28, CYP3A5*3, CYP3A4*1G, ABCB1 C3435T were in Hardy–Weinberg equilibrium ($p > 0.05$). Mutant alleles and genotype frequencies are described in Table 2.

**Amlodipine concentrations:** A total of 228 plasma concentrations of amlodipine are available for population modeling (Fig. 1). On the sampling day, the mean plasma concentrations of amlodipine at 0, 2, 6, and 24 h were 7.32 ± 3.34 ng/ml, 8.95 ± 4.00 ng/ml, 10.91 ± 4.61 ng/ml and 7.51 ± 3.21 ng/ml. Drug concentrations distributed in the absorption phase, distribution phase and elimination phase.

**Population pharmacokinetic analysis:**

**Model development**

Multiple structural models were explored to determine the model that best fit the amlodipine concentration data. One-compartment and two-compartment models with zero-order and first-order absorption models with and without absorption lag time were compared. We found that amlodipine pharmacokinetic data were adequately shown by a one-compartment model with first-order elimination and absorption. The parameters estimated were the absorption rate constant ($K_a$), oral clearance ($CL/F$), and apparent volume of distribution ($V/F$). Exponential and proportional plus additive error models were used to appropriately describe the inter-subject and residual variabilities, respectively.

**Covariate analysis**

In the forward model building step, adding GNDR, ABCB1 C3435T genotypes and TP to CL/F decreased the OFV by more than 3.84 ($p < 0.05$) at each addition. Adding ABCB1 C3435T to V/F also decreased the OFV significantly. GNDR on CL/F and ABCB1 C3435T on V/F of amlodipine appeared to be the most important influential covariates.

In the final backward elimination step, a significant increase in OFV by more than 7.88 ($p < 0.005$) was observed on elimination of GNDR and ABCB1 C3435T from the model. However, 0 fell in the 95% confidence interval of the typical value of the effect of ABCB1 C3435T on V/F, therefore we removed it from the final model. The covariate modeling process is shown in Table 3. CL/F
was affected by gender and ABCB1 C3435T genotype, illustrated in the following equation:

\[
CL_{Fi} = 28.8 \times (1 + \text{GNDR})^{-0.531} \times (\text{ABCB1} \ C3435T),
\]

where ABCB1 3435TT is 1.503 for individuals with lower enzymatic activity of ABCB1. The parameters for the final covariate model for the CL/F of amlodipine are shown in Table 4.

The CL/F of amlodipine in male or subjects with ABCB1 3435TT genotype is greater than that in female or ones with ABCB1 3435CC or CT genotype. The model estimates that a female subject with ABCB1 3435TT genotype would have a CL/F of 30.0 L/h. The residual error model indicated that an additive term in addition to the proportional error term was applicable to the study.

Model validation

Figure 2 shows the goodness-of-fit plots for the final amlodipine 1-compartment model. The individual- and population-predicted plasma amlodipine concentrations matched the observed plasma amlodipine concentrations, demonstrating that the model adequately described the data. The CWRES showed a random distribution around zero and 95% of them were within an acceptable range (−2 to 2).

The final model was subjected to bootstrap analysis. The mean parameter estimates and percentile-based bootstrap 95% CIs obtained from 1,000 runs are presented in Table 4. Minimization and the covariance step were successful in 100.0% and 87.3% of bootstrap runs, and the mean parameter estimates were not statistically different from the estimates obtained using the original dataset. The model is also stable because the variability estimates obtained from bootstrap analysis are close to those obtained from the original dataset.

Figure 3 shows a SVPC of the pharmacokinetic model for amlodipine after oral administration to adult patients with mild
to moderate essential hypertension. The open circles represent calculated $P_{ij}$ for each observation versus time, obtained from 1,000 simulated datasets.

**Exposure-response analysis for SBP:** Figure 4 shows the relationship between changes in systolic blood pressure on about day 28 from its baseline and the AUC of amlodipine. Exploratory plots indicated that a linear model was preferable for modeling the dependence of SBP on amlodipine exposure. The coefficient of correlation between them was 0.534 ($p < 0.05$).

**Discussion**

A 1-compartment linear model with first-order absorption...
and elimination was found to be the best structural model for amlodipine in the present study. This is in agreement with findings in previous studies.\textsuperscript{12,13} Gender and ABCB1 genotype significantly affected the CL/F of amlodipine. Lower CL/F and higher exposure occurs in female subjects with the ABCB1 3435CC or CT genotype. The population values of CL/F for a subject in this study were 28.8 L/h and 19.9 L/h for males and females, respectively, which is consistent with previous reports that hypertensive child and adolescent subjects have CL/F values of 23.7 L/h in males and 17.6 L/h in females\textsuperscript{12} and, is also similar to 23.0 L/h and 20.8 L/h calculated by lean body weight in males and females with mean ages greater than 70 years, respectively.\textsuperscript{14}

The frequencies of ABCB1 3435CC, CT and TT are 0.5, 0.4 and 0.1, which is similar to the report on Chinese hypertensive patients.\textsuperscript{15} Higher CL/F of amlodipine was observed in subjects carrying ABCB1 3435TT in the present study. This is consistent with the report that 3435TT genotypes increased the amlodipine consumption.\textsuperscript{3} That is to say, subjects with the ABCB1 3435TT genotype need higher dose of amlodipine to obtain the same antihypertensive effect as the ABCB1 3435CC and CT genotype groups.

It has been reported that P-gp was widely distributed in several human tissues, including liver, intestine, pancreas and kidney.\textsuperscript{16} The polymorphism in exon 26 (C3435T) of MDR-1 is related to the decreased protein expression and function, and affects the absorption and tissue concentrations of the substrate of MDR-1.\textsuperscript{17} The expression level of P-gp was higher in ABCB1 3435CC or 3435CT subjects than in 3435TT ones. Low P-gp activity in the liver leading to higher absorption of amlodipine in intrahepatocellular is suggested to result in increased hepatic CYP3A metabolism for co-substrates of CYP3A and P-gp.\textsuperscript{18} This may explain our results that the CL/F of amlodipine in subjects with the ABCB1 3435TT genotype is higher than that in subjects with the ABCB1 3435CC or 3435CT genotype. Our findings showed that the oral clearance of amlodipine was 1.50-fold higher in participants carrying the ABCB1 3435TT genotype than in individuals with the ABCB1 3435CT or 3435CC genotype, which is similar to previous reports.\textsuperscript{8,19} However, the effect of ABCB1 genetic variants on pharmacokinetics of other P-gp substrates remains controversial.\textsuperscript{19,20} ABCB1 haplotype-based analysis of the population pharmacokinetics of amlodipine derived from G267TT/C3435T still need to be further investigated in a large scale population.

Females possessing the 2677TT-3435TT haplotype have higher CYP3A4 mRNA expression levels (median, 10.7; range, 5.92–15.2 amol/µg total RNA) than those with 2677GG-3435CC (median, 3.03; range 1.38–4.68) or 2677GT-3435CT (median, 4.31; range, 0.07–9.42) (p = 0.022).\textsuperscript{21} In addition, previous surveys using mdr1a (−/−), mdr1b (−/−) and mdr1a/1b (−/−) mice housed in Amsterdam have identified that the mice lacking P-gp are capable of inducing CYP3A expression in hepatocytes.\textsuperscript{22} The most extensively studied CYP3A5 SNP, designated as CYP3A5*1, expresses a high level of functional CYP3A5 protein in subjects with CYP3A5*1/*1 or CYP3A5*1/*3 genotypes and very low or undetectable levels of functional CYP3A5 protein in ones with CYP3A5*3/*3 genotypes. Zhao et al.\textsuperscript{23} showed that CYP3A5*3/*3 was linked with a significant increase in Cmax and AUC\textsubscript{0–∞} of nimodipine, although our previous study\textsuperscript{24} indicates that the CYP3A5*1 allele is an important factor in the disposition of amlodipine in a single-dose study, which is in agreement with Kim’s report,\textsuperscript{25} the CYP3A5 genotype was not brought into the final model.

The CYP3A4*1G mutant allele, occurring at a frequency of 0.30 in Chinese renal transplant recipients,\textsuperscript{26} might be related to the higher CYP3A4 enzyme activity,\textsuperscript{10,26} while CYP3A4*1G expression seemed to increase the effect of atorvastatin, probably resulting from a lower enzymatic activity of the CYP3A4*1G allele.\textsuperscript{27} POR is the only flavoprotein that donates electrons to microsomal P450 enzymes. POR\textsuperscript{28} C-T polymorphism was associated with CYP3A activity.\textsuperscript{28,29} Our results did not show any significant effect of POR*28, CYP3A4*1G or CYP3A5*3 variants on the disposition of amlodipine in essential hypertensive patients. The major reason is that a study involving a larger population sample is needed to take into account genetic linkage analysis between CYP3A4*1G and CYP3A5*3 on the biotransformation of amlodipine.

This study shows that gender is an important factor in the disposition of amlodipine. The CL/F of amlodipine in the hypertensive female patients is less than that in male patients, which is line with previous studies.\textsuperscript{12–14} Thus, amlodipine concentrations were higher in women than men and the decrease in BP with amlodipine was greater within the female group, similar to the literature.\textsuperscript{30,31} These findings may be partly explained by the research done by Wolbold et al.\textsuperscript{12} Although CYP3A4 is differentially expressed between the two genders, with women expressing about twice the amount of the enzyme on the basis of microsomal protein content and faster clearance of CYP3A substrates in women, treatment with newer calcium antagonists such as amlodipine, felodipine and nitrendipine was associated with an average reduction of CYP3A4 expression by 45%. Therefore, it is likely that female patients receiving amlodipine or other long-acting calcium antagonists would have a significantly lower CYP3A4 expression than males. In addition, the gender distribution and body weight are significantly correlated and the correlation coefficient is −0.51, which is consistent with Rohatagi et al.’s report.\textsuperscript{13} Thus, the effect of gender on the pharmacokinetics of amlodipine may be partly explained by the weight difference between males and females. This needs to be clarified by a large-scale population study.

Our investigation suggested a positive relationship between the difference in SBP from pre- and post-dose of amlodipine and the steady-state AUC of amlodipine. The influencing factors of the ABCB1 C3435T variant and gender on the pharmacokinetics of amlodipine would have similar effects on the pharmacodynamics in hypertensive patients. This suggests that a greater BP response in female than male patients may be explained by the lower CL/F and higher drug exposure of amlodipine in the female group, similarly to the effect of the ABCB1 C3435T allele on drug exposure and BP response described above. Because only the baseline and the terminal point value of SBP and DBP were recorded, an exposure-response model could not be obtained due to the lack of convergence. Further studies need to investigate the exact prediction of change in SBP or DBP treatment with amlodipine.

In conclusion, this is the first study to extensively investigate the effect of ABCB1 C3435T, POR*28, CYP3A4*1G and CYP3A5*3 variants and gender on the disposition of amlodipine in essential hypertensive patients. The study results suggest that ABCB1 C3435T polymorphism and gender are determinant factors of amlodipine pharmacokinetic variability. Lower CL/F and higher exposure occurs in female subjects with the ABCB1 3435CC or
CT genotype who have greater decreases in blood pressure after treatment with amlodipine. Thus, a higher dosage needs to be administered to males with the ABCB1 3435TT genotype to achieve a better antihypertensive effect. The results may be good administered to males with the ABCB1 3435TT genotype to CT genotype who have greater decreases in blood pressure after and tolerability of amlodipine in essential hypertensive patients. 14) Kang, D., Verotta, D. and Schwartz, J. B.: Population analyses of 16) Thiebaut, F., Tsuruo, T., Harnada, H., Gottesman, M. M., Pastan, I. and Willingham, M. C.: Cellular localization of the multidrug-resistance gene

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