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Relationship between genetic polymorphisms of drug efflux transporter MDR1 (ABCB1) and response to losartan in hypertension patients

M.T. GÖKTAŞ[1], F. PEPEDIL[2], Ö. KARACA[3], S. KALKIŞIM[3], L. CEVIK[3], E. GUMUS[3], G.S. GUVEN[2], M.O. BABAOGLU[3], A. BOZKURT[4], U. YASAR[3]

[1]Department of Pharmacology, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey
[2]Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[3]Department of Pharmacology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[4]Department of Pharmacology, Faculty of Medicine, BAU International University, Batumi, Georgia

Abstract. – OBJECTIVE: Losartan is a selective angiotensin II receptor type 1 blocker and a substrate of drug efflux transporter *MDR1* (ABCB1). *MDR1* shows inter-individual variations due to genetic polymorphisms. *C3435T*, *G2677T* and *C1236T* polymorphic alleles of the MDR1 gene encoding the transporter have been shown to alter the transport, bioavailability and efficacy of certain drugs. The purpose of this study was to investigate the relationship between genetic polymorphisms of *MDR1* (*C3435T*, *G2677T/A* and *C1236T*) and response to the treatment in newly diagnosed hypertensive patients being treated with losartan.

PATIENTS AND METHODS: A total of 74 newly diagnosed hypertension patients were included in the study. Genotyping was performed using PCR-RFLP. Systolic and diastolic mean blood pressure changes of the patients were expressed as a percentage (± SD). Blood pressure values prior to initiation of the treatment and subsequent measurements 6 weeks after starting the treatment were compared.

RESULTS: Regarding the *C3435T* polymorphism, a mean decrease of systolic blood pressure in individuals with *CT* or *TT* genotype (n= 55; 11.6% ± 9.7 mmHg) was significantly higher compared with that of the CC genotype (n = 19; 6.7% ± 9.6 mmHg, p = 0.03). No significant systolic blood pressure changes observed in *G2677T/A* and *C1236T* genotypes (p = 0.13 and 0.07, respectively). There was not any significant difference in diastolic blood pressure changes between pre- and post-treatment for any of the genotypes with *C3435T*, *G2677T/A*, or *C1236T* variations.

CONCLUSIONS: This study revealed that hypotensive response to losartan was significantly affected by the C3435T genetic polymorphism of MDR1 and hypertensive patients with MDR1 3435T allele may present a better response to losartan treatment.

Key Words:
P-glycoprotein, MDR1, Genetic polymorphism, Hypertension, Losartan.

Introduction

ATP-binding cassette sub-family B member 1 (ABCB1, MDR1, P-glycoprotein) is a transporter protein that is responsible for the efflux of many drugs in various cells in human body[1-3]. Multidrug resistance 1 (*MDR1*) gene is expressed mainly in the proximal tubule of the kidney, intestine, placenta, central nervous system (CNS), pancreas, testis, liver, and cancer cells[4]. Many drug molecules such as antihypertensive and antineoplastic agents, HIV protease inhibitors, immunosuppressant agents and antiarrhythmic drugs are MDR1 substrates[5-7]. MDR1 is a highly polymorphic transporter and more than 50 single nucleotide polymorphisms (SNPs) have been identified[8,9]. The variations in the *MDR1* gene can affect absorption, tissue distribution and response to the therapy with these drugs[10]. Several studies investigated three most common SNPs of *MDR1 C3435T*, *G2677T/A* and *C1236T*. The *C3435T* and *C1236T* are wobble mutations. *C3534T* variant is a *C* to *T* transition in exon 26, and *C1236T* is a *C* to *T* substitution in exon 12[11]. The *G2677T/A* is located in exon 21 and results in a *G* to *T/A* transition. The polymorphisms of *ABCB1 C3435T, G2677T/A* and *C1236T* have been shown to be associated with altered clinical efficacy of drug treatment[12-15].

Losartan is an angiotensin II type 1 receptor (AT1) antagonist used for the treatment of hypertension as well as other cardiovascular dis-

Corresponding Author: Mustafa Tugrul Goktas, MD; e-mail: dr_tugrul084@hotmail.com

eases[16,17]. Losartan is mainly metabolized by cytochrome P450 2C9 (CYP2C9) to its active metabolite E-3174[18]. It has been demonstrated that different polymorphic variants of *CYP2C9* affect the metabolism of losartan in varying degrees[19-21]. Soldner et al[7] determined that losartan was a substrate for the ABCB1 transporter in an *in vitro* study. The active metabolite of losartan, E-3174, which is the main substance responsible for the pharmacological effects was not found to be a substrate of MDR1[7].

The association between the polymorphisms of *ABCB1* and response to losartan treatment in hypertensive patients has not been reported previously. The purpose of this study was to investigate the relationship between the *ABCB1 C3435T G2677T/A* and *C1236T* polymorphisms and hypotensive response to losartan.

Patients and Methods

Patients aged over 18 years old with newly diagnosed essential hypertension (phase I) were recruited into the study at the General Internal Medicine Unit, Hacettepe University Hospital. Patients using drugs with antihypertensive efficacy for various reasons at the time of application, with blood pressures higher than 160/100 mmHg and necessitating therapy with more than one drug according to current guidelines were excluded. History of chronic diseases, drug utilisation, smoking and alcohol consumptions were recorded. All routine laboratory tests such as fasting lipid profile in blood, fasting blood glucose, liver and kidney function tests, presence of micro-albumin in the 24-hour urine, electrocardiography, echocardiography and eye examinations for retinopathy were performed for each patient. All subjects in the study started to receive 100 mg of losartan treatment. After six weeks, blood pressure was measured again, compared with the initial blood pressure values, and the change in blood pressure was recorded. Blood pressure was measured at rest in sitting position with a mercury sphygmomanometer. All measurements were performed at least two times with minimum five-minute intervals from each arm and the mean of two measurements were calculated. For the diagnosis of hypertension, patients with blood pressure higher than 140/90 mm Hg were invited again a week later and the blood pressure measurements were assessed in the same way. Blood pressures of all patients were measured by the same person with the same sphygmomanometer device. Each patient was evaluated for the lifestyle changes and compliance with the drug use. The study was approved by the Hacettepe University School of Medicine Ethics Committee (08/06-3) and written and oral informed consents were obtained from all patients.

Genotyping for MDR1 C3435T, G2677T/A and C1236T Variants

Blood samples taken from the patients were kept in the tubes with ethylene diamine tetraacetic acid (EDTA) at -20°C until DNA isolation. Genomic DNA was isolated by QIAamp DNA Genomic DNA extraction kit (Qiagen, Hilden, Germany). Genotyping for the MDR1 polymorphisms was performed according to the methods previously described by Cascorbi et al[8] (Table I) for C3435T and G2677T/A with minor modifications and our method for C1236T. PCR was performed in a total volume of 25 μL containing 1 unit Taq polymerase enzyme, 0.5 μM of each primer, 100 ng of DNA, 200 μM of dNTP

Table I. Primers and enzymes used for the genotyping of *MDR1* variants *C3435T*, *G2677T/A* and *C1236T*.

MDR1 polymorphism	Primer	PCR product	Enzyme	Variant	Cleavage products (bp)
C3435T	5′-TGT TTT CAG CTG CTT GAT GG-3′	197	MboI	C	158+39
	5′-AAG GCA TGT ATG TTG GCC TC-3′			T	197
G2677T	5′-TGC AGG CTA TAG GTT CCA-3′	224	BanI	G	198+26
	5′-TTT AGT TTG ACT CAC CTT CCC G-3′			T, A	224
G2677A	5′-TGC AGG CTA TAG GTT CCA GG- 3′	220	BsrI	G, T	220
	5′-GTT TGA CTC ACC TTC CCA G- 3′			A	206+14
C1236T	5′-TGG ACT GTT GTG CTC TTC CC-3′	455	HaeIII	C	377+43+35
	5′-TGT CAC TTT ATC CAG CTC TCC A- 3′			T	412+43

mixture. The PCR conditions were as follows: initial denaturation at 95°C for 2 min, followed by 35 cycles of 30 s at 94°C, 30 s at 60°C, 30 s at 72°C, and a final extension at 72°C for 7 min. Primers and restriction enzymes used to assess polymorphisms and fragments generated by each PCR-RFLP method are shown in Table I. The prepared mixture was allowed to stand overnight for restriction reactions and resulting products were analysed by using 3% agarose gel electrophoresis.

Statistical Analysis

Differences in the changes of systolic and diastolic blood pressure between the genotype and haplotype groups were compared using Student's *t*-test. In all analyses, the *p*-value was considered statistically significant if < 0.05. The data was shown as the mean ± standard deviation (SD). GraphPad Prism Version 6.01 for Windows (San Diego, CA, USA) was used for statistical analysis.

Results

Among 74 newly diagnosed hypertensive patients that accepted to participate in the study, 54 patients (73.0%) were female and 20 patients (27.0%) were male. The mean (± SD) age of the study group was 48.3 ± 7.4 years. The main clinical features of the patients were as follows: Four patients had type II diabetes mellitus and 3 patients were pre-diabetic. The fasting blood glucose levels for the remaining 67 patients were within the normal values. Twenty-four-hour urine samples of 55 patients were examined and micro albuminuria was detected in five patients. Echocardiography of 70 patients demonstrated left ventricular hypertrophy in two patients, diastolic dysfunction in six patients, rheumatic heart disease, atrial septal defect and coronary artery diseases in only one patient. The other 59 patients had no abnormality in echocardiography. Ophthalmic examination of 70 patients showed no pathology in 53 patients, stage 1 hypertensive retinopathy was observed in 17 patients. Biochemical parameters of the patients are summarised in Table II.

Table II. Biochemical parameters of the patients participating in the study (n = 74).

Variable	Value (mean ± SD)
Creatinine (mg/dl)	0.53 ± 0.15
Creatinine clearance (ml/min)	113 ± 23
Fasting blood sugar (mg/dl)	94 ± 18
Triglycerides (mg/dl)	145 ± 79
LDL (mg/dl)	118 ± 29
HDL (mg/dl)	54 ± 12
Body Mass Index (kg/m^2)	29.4 ± 3.9

The frequencies of alleles and genotypes of the *MDR1* C*3435T,* G*2677T/A* and *C1236T* are listed in Table III. The *CT* (47.3%), *GT* (43.3%), and *CT* (42.3%) genotypes were the most common variants for the *C3435T*, *G2677T/A*, *C1236T* polymorphisms, respectively. The most common alleles were *T* (50.7%), *G* (51.4%), and *C* (54.9%), respectively. The frequency of the all-wild (*CC-GG-CC)* haplotype was 18.3% and all-variant (*TT-TT-TT)* haplotype was 21.1%.

Table III. Genotype, allele and haplotype distribution of the *MDR1 C3435T*, *G2677T/A*, and *C1236T* variants in hypertensive patients (n = 74).

	MDR1 3435 genotype			MDR1 2677 genotype			MDR1 1236 genotype		
	C > T	n (%)	95% CI	aG > T/A	n (%)	95% CI	C > T	n (%)	95% CI
Genotype	CC	19 (25.6)	17-34.2	GG	21 (28.4)	19.6-37.2	CC	24 (33.8)	24.5-43.1
	CT	35 (47.3)	37.5-57.1	GT	32 (43.3)	33.6-53	CT	30 (42.3)	32.6-52
	TT	20 (27.1)	18.4-35.8	GA	2 (2.7)	0-5.9	TT	17 (23.9)	15.5-32.3
				TT	18 (24.3)	15.9-32.7			
				TA	1 (1.3)	0-3.5			
Allele	C	73 (49.3)	39.5-59.1	G	76 (51.4)	41.6-61.2	C	78 (54.9)	45.1-64.7
	T	75 (50.7)	40.6-60.5	T	69 (46.6)	36.8-56.4	T	64 (45.1)	35.3-54.9
				A	3 (2)	0-4.7			
Haplotype	CC-GG-CC	13 (18.3)	10.7-25.9						
	TT-TT-TT	15 (21.1)	13.1-29.1						

Table IV. Differences in blood pressure levels between the measurements of before and after the losartan treatment.

Blood pressure	Before treatment	95% CI	After treatment	95% CI	Decrease of blood pressure (%)	95% CI
Systolic (mmHg)	150.9 ± 8.3	149-152.8	135.1 ± 14.9	131.7-138.5	10.4 ± 9.9	8.1-12.6
Diastolic (mmHg)	94.5 ± 6.9	92.9-96	86.3 ± 9.1	84.2-88.4	8.1 ± 12.1	5.4-10.9

Before starting the losartan treatment, mean (± S.D.) systolic and diastolic blood pressures were 150.9 ± 8.3 mmHg and 94.5 ± 6.9 mmHg, respectively (Table IV). Six weeks after treatment, average systolic and diastolic blood pressures were 135.1 ± 14.9 and 86.3 ± 9.1 mmHg, respectively (Table IV). Systolic and diastolic blood pressures of the patients were compared within the *MDR1 C3435T, G2677T/A* and *C1236T* genotype and haplotype groups (Figure 1-2).

Decrease in systolic blood pressures were 6.7 ± 9.6%, and 11.6 ± 9.7% in the *MDR1 3435 CC* genotype group and the group containing at least one variant allele (*CT*+*TT*), respectively (Figure 1A, $p = 0.03$). The systolic decreases were 8.3 ± 9.4% and 11.2 ± 10.7% in the *MDR1 2677 GG* genotype group versus the group with other variants, respectively (Figure 1B, $p = 0.13$). The reduction in systolic blood pressure in the *MDR1 1236* genotype groups were 8.0 ± 9.0% and 11.8

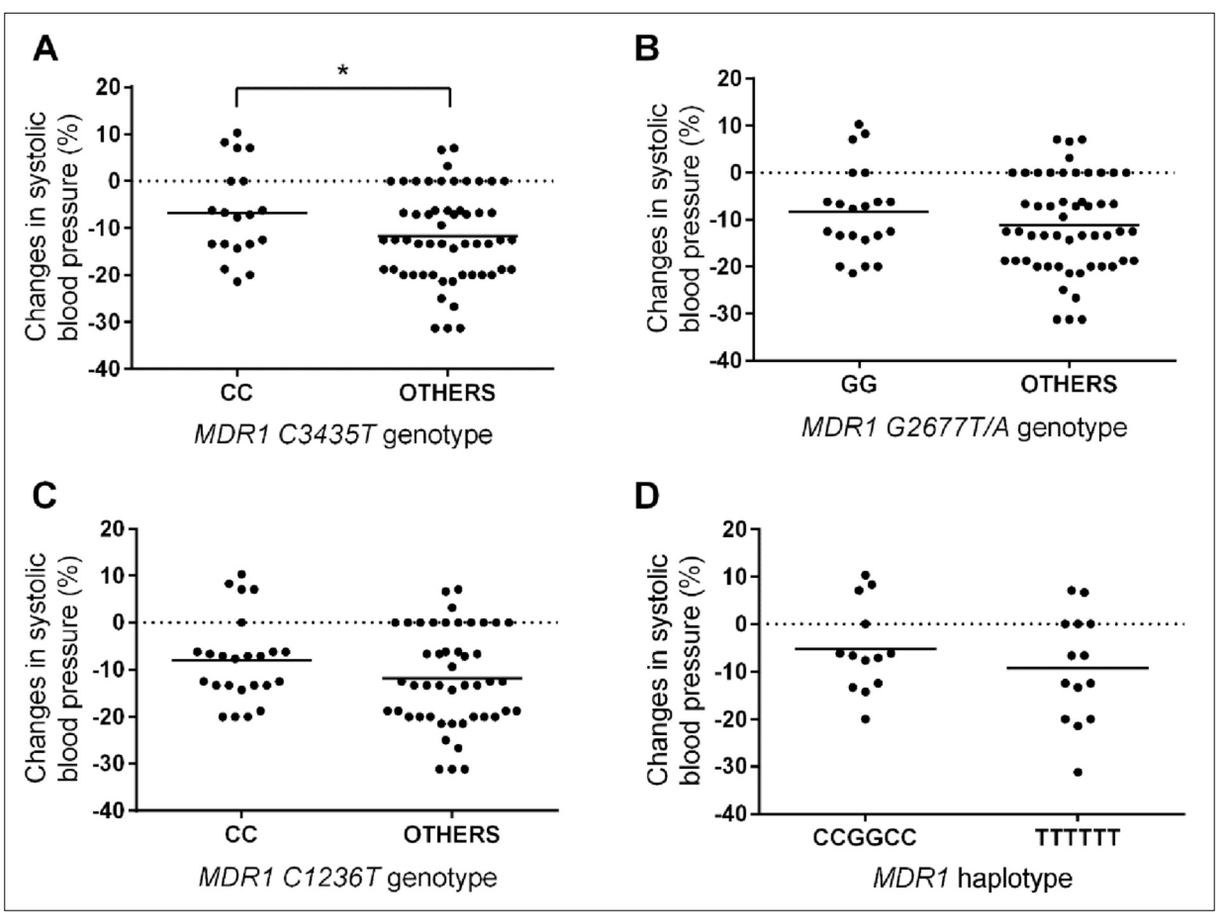

Figure 1. Changes of systolic blood pressure of *MDR1 C3435T* ***(A)***, *G2677T/A* ***(B)***, *C1236T* ***(C)*** genotypes and haplotype ***(D)*** groups. Mean of each groups indicated. (A: 3435 CC was compared with *CT* and *TT* genotype, $*p = 0.04$. B: 2677 GG was compared with *GT*, *GA*, *TA* and *TT* genotype, $p = 0.13$. C: 1236 *CC* was compared with *CT* and *TT* genotype, $p = 0.06$ D: *MDR1 CC-GG-CC* haplotype compared with *TT-TT-TT*, $p = 0.19$).

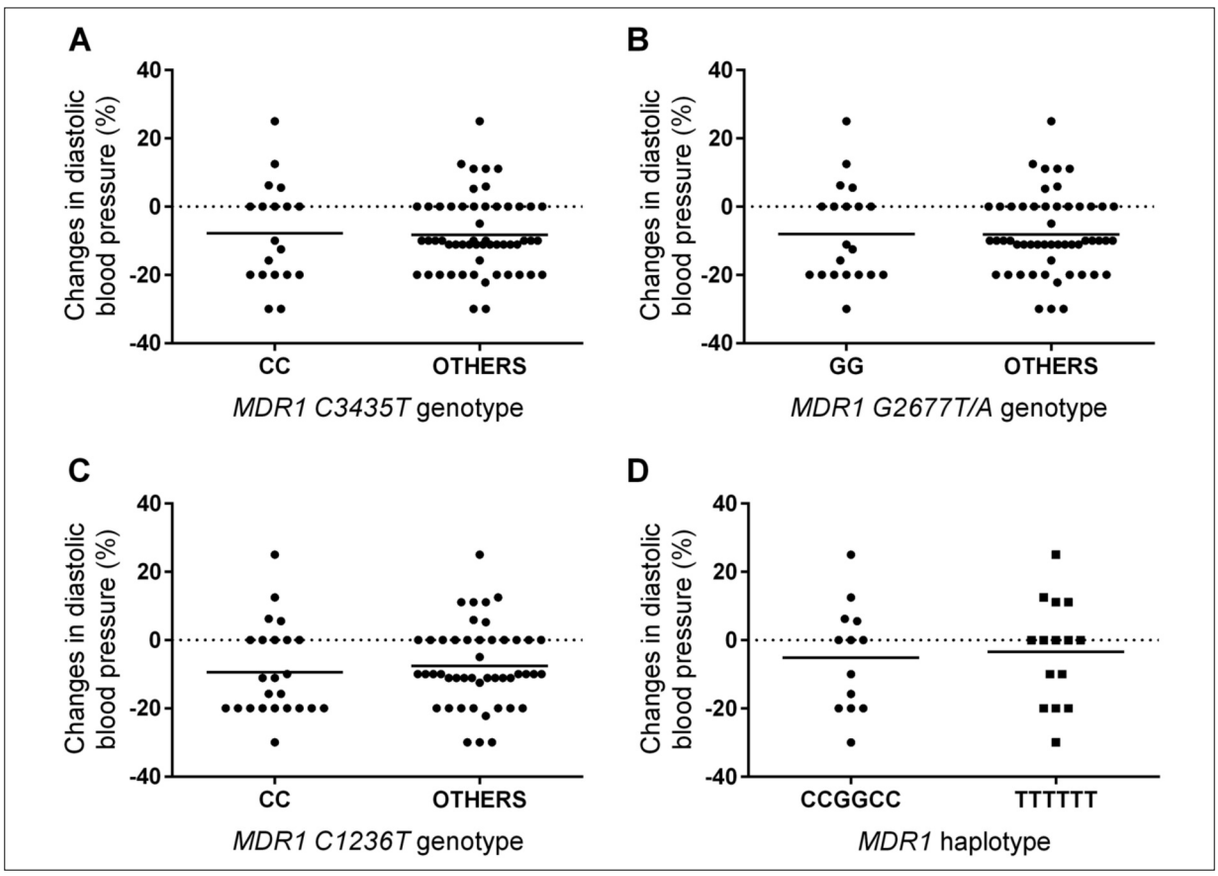

Figure 2. Changes of diastolic blood pressure of *MDR1 C3435T* ***(A)***, G2677T/A ***(B)***, *C1236T* ***(C)*** genotypes and haplotype ***(D)*** groups. Mean of each groups indicated. (A: 3435 *CC* was compared with *CT* and *TT* genotype, $p = 0.46$. B: 2677 *GG* was compared with *GT*, *GA*, *TA* and *TT* genotype, $p = 0.49$. C: 1236 CC was compared with *CT* and *TT* genotype, $p = 0.39$. D: *MDR1 CC-GG-CC* haplotype was compared with *TT-TT-TT*, $p = 0.38$).

± 10.3% for the *CC* and *CT-TT* variant groups, respectively (Figure 1C, $p = 0.07$).

The decrease of diastolic blood pressures were 7.8 ± 14.9% and 8.2 ± 11.1% among the *MDR1 3435 CC* and *CT-TT* genotype groups, respectively (Figure 2A, $p = 0.45$). Changes of diastolic blood pressures were 8.1 ± 13.8 and 8.2 ± 11.5% in the *MDR1 2677 GG* genotype group versus other variants (Figure 2B, $p = 0.50$). Reduction in diastolic blood pressures were 9.4 ± 13.4% and 7.6 ± 11.9% in *MDR1 1236 CC* and *CT-TT* genotype groups, respectively (Figure 2C, $p = 0.29$).

The *TT-TT-TT* haplotype group for MDR1 variants had a higher change of systolic blood pressure than *CCGGCC* haplotype group (8.7 ± 11.3% and 5.3 ± 9.3%, Figure 1D) but this difference was not statistically significant (p=0.20). The changes for the diastolic blood pressures were 3.4 ± 15% and 5.1 ± 15.7%, respectively (Figure 2D, $p = 0.38$).

Discussion

This study showed that in hypertension patients using losartan as a single drug, change in systolic but not diastolic blood pressures before and 6 weeks after treatment were affected from MDR1 C3435T genetic polymorphism, and the patients with mutant allele (3435 CT/TT) showed a significantly higher clinical response. MDR1 *G2677T/A, C1236T* polymorphisms and MDR1 haplotypes did not affect the decrease in systolic blood pressure after drug treatment. Change in diastolic blood pressure in MDR1 *C3435T, G2677T/A, C1236T* genotype and haplotype groups were similar. Despite the large amount of research on other drug substrates of MDR1, there is no study investigating the relationship between MDR1 polymorphisms with losartan treatment in hypertensive patients. To our knowledge, this is the first work that showed such an association.

Limited information is available in the literature with pharmacogenetics of angiotensin II receptor antagonists in human. For example; *C3435T* polymorphism does not seem to have an effect on blood pressures in the hypertensive renal transplant patients using valsartan[22]. In another report, *C3435T* polymorphism did not affect Telmisartan pharmacokinetics in 19 Chinese healthy volunteers[23].

There are many studies that examined the response of drugs and therapies used in various diseases with MDR1 genetic polymorphisms in the literature[24]. Over 50 MDR1 genetic polymorphisms were investigated and their functional importance and frequency in different ethnic groups were studied. C3435T, G2677T/A and C1236T polymorphisms have been shown to be prevalent in various ethnic groups[25]. This study shows similarity to others in Turkish population in terms of genotype and allele distributions[26].

Previously, Yasar et al[26] showed that MDR1 *C3435T* polymorphism did not significantly change the metabolic ratio of losartan among genotype groups[26]. We showed that MDR1 *3435T* allele carriers (*CT* or *TT* subjects) had a better response to losartan as compared to MDR1 *3435 CC* carriers. The findings of these two studies seem to be in contrast to each other. However, our present study investigated the long-term (6-weeks) clinical effects of losartan treatment while in the previous study by Yasar et al[26] only a single dose of losartan was used for phenotyping purposes and the effect of losartan on blood pressure was not evaluated. Guo et al[27] reported that MDR1 *C3435T* genetic polymorphisms significantly affected plasma concentrations of amlodipine, but the antihypertensive response to amlodipine was not affected. Cai et al[22] also showed that MDR1 *C3435T* genetic polymorphism did not affect the therapeutic response of amlodipine and valsartan in hypertensive patients.

MDR1 *C3435T* polymorphism affected change in systolic blood pressure after 6 weeks of losartan treatment without altering the metabolic ratio of losartan. Additional to the effect of MDR1 on losartan distribution in tissues, this effect of MDR1 *C3435T* polymorphism may also be associated with endogenous ouabain which is an adrenocortical hormone. Blaustein et al[28] reported that hypertensive patients had higher plasma endogenous ouabain concentrations, which may be an effective factor in the pathophysiology of hypertension. Tripodi et al[29] observed that MDR1 *3435 CT* or *TT* genotype carriers had significantly higher plasma endogenous ouabain concentrations than MDR1 3435 *CC* genotype carriers in untreated hypertension patients. Zolk et al[30] showed that MDR1 3435 *TT* genotype carriers had a higher change in plasma aldosterone concentrations than the other genotype groups after administration of angiotensin II in individuals with normal blood pressure. Therefore, MDR1 *3435T* allele carriers may be more sensitive to antihypertensive therapy with losartan.

Conclusions

MDR1 *C3435T* polymorphism had a significant effect on systolic, but not diastolic, blood pressure decrements in hypertensive patients treated with losartan long-term. Further clinical studies in different populations are warranted to support or not to support these findings.

Ethical Statement

Ethical Approval was taken according to Declaration of Helsinki. Approval (Ethical Principles for Medical Research Involving Human Subjects) was taken with the paper number of "Hacettepe University School of Medicine Ethics Committee (08/06-3)".

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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