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ORIGINAL RESEARCH

Influence of CYP450 Enzymes and ABCB1 Polymorphisms on Clopidogrel Response in Moroccan Patients with Acute Coronary Syndromes

Ismail Mouhrach[1,2], Laila Bouguenouch[2,3], Adil Kamal[3,4], Abbassi Meriame[2], Nada El Khorb[3,4], Mohammed El Azami El Idrissi[3], Hafid Akoudad[3,4], Hicham Bekkari[1]

[1]Laboratory of Biotechnology, Environment, Agrifood, and Health, Faculty of Sciences Dhar El Mahraz, Sidi Mohamed Ben Abdellah University, Fez, Morocco; [2]Department of Medical Genetics and Oncogenetics, University Hospital Hassan II, Fez, Morocco; [3]Faculty of Medicine and Pharmacy, Sidi Mohamed Ben Abdellah University, Fez, Morocco; [4]Department of Cardiology, University Hospital Hassan II, Fez, Morocco

Correspondence: Ismail Mouhrach, Laboratory of Biotechnology, Environment, Agrifood, and Health, Faculty of Sciences Dhar El Mahraz, Sidi Mohamed Ben Abdellah University, B.P. 1796 Fès-Atlas, Fez, 30003, Morocco, Tel +212 7 08 02 96 10, Fax +212535642500, Email ismail.mouhrach@usmba.ac.ma

Introduction: Clopidogrel is an antiplatelet prodrug primarily prescribed to prevent or treat acute coronary syndrome (ACS) or acute ischemic stroke (IS), polymorphisms of genes encoding cytochrome P-450 (CYP) and P-glycoprotein transporter, could affect the efficiency of clopidogrel absorption and biotransformation, especially during the first critical hours following its administration.

Methods: The present study was designed to investigate the potential association of clopidogrel responsiveness and 14 polymorphisms in the genes encoding the CYPs (CYP2C9, 2C19, 3A4, 3A5, 1A2, and 2B6), the ATP binding cassette subfamily B member 1 (ABCB1). Platelet aggregation activity was measured after 8h of 300mg clopidogrel administration for fifty-five ACS patients.

Results: There was no significant association between polymorphism of the studied CYPs and clopidogrel responsiveness (P>0.05). The frequency of the ABCB1 3435 T allele in clopidogrel non-responders was higher (78.9%) compared to responders (52.8%), but this difference was not significant (P=0.057). Demographic characteristics, comorbidities, concomitant treatments were not associated with clopidogrel response.

Discussion: There was no effect of the studied genetic variations and demographic factors on the platelet activity of clopidogrel in Moroccan ACS patients.

Keywords: clopidogrel resistance, coronary artery disease, gene polymorphisms, platelet inhibitors, ABCB1 gene, CYP450 gene

Introduction

Cardiovascular disease is the major cause of death worldwide. Acute coronary syndromes (ACS) refer to a spectrum of clinical presentations including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina. The cornerstone of therapy is represented by antithrombotic therapy including antiplatelet therapy. Clopidogrel which is an antiplatelet drug inhibiting P2Y12 receptors is widely prescribed in the setting of acute coronary syndromes especially in developing countries.[1,2]

However, the capacity of clopidogrel to inhibit ADP-induced platelet aggregation varies among subjects. This variability may reflect genetic polymorphisms in the enzymes involved in the metabolic activation of clopidogrel. Patients with polymorphisms in ATP-binding cassette subfamily B member 1 (ABCB1) may also exhibit impaired absorption of clopidogrel. These situations refer to clopidogrel resistance which has been associated with ischemic complications after percutaneous coronary intervention including myocardial infarction and stent thrombosis[3] It is already known that genetic polymorphisms can explain numerous situations associated with clopidogrel resistance. In a Moroccan study of healthy subjects, showed that the ABCB1 genotypic frequencies were 39% for 3435 CC, 51% for 3435 CT, and 10% for 3435 TT.[4] Nevertheless, there are not many studies having studied this resistance in African or Arab populations.

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Previous reports have suggested that clopidogrel therapy is not always efficient, it is marked by considerable inter-patient variability due to genetic and environmental components.[5] The response to clopidogrel depends on its absorption in the intestine and its metabolism in the liver.[6] Several polymorphisms are associated with clopidogrel response. For instance, variation in the ABCB1 gene encoding the intestinal efflux transporter known as P-glycoprotein (P-gp) have been associated with decreased Clopidogrel absorption.[3–7]

After absorption, the Clopidogrel prodrug requires biotransformation into its active form by several hepatic cytochrome p450 (CYP) isoenzymes, encoded by CYP2C9, 2C19, 3A4, 3A5, 1A2, and 2B6 genes.[8] Variants in the most studied gene CYP2C19 have been identified to be strong predictors of clopidogrel response.[6–9] CYP2C19 intermediate and poor metabolizer phenotypes (IM and PM) have been associated with lower platelet inhibition and increase the risk of adverse cardiovascular events in patients treated with clopidogrel, whereas the CYP2C19 ultrarapid metabolizer (UM) phenotype has been linked to increased platelet inhibition.[3–11] Additionally, other factors including epigenetics, demographics, disease complications and drug-drug interactions may also contribute to the poor clopidogrel response.[8]

Fast and significant response to clopidogrel following the first hours of administration, is an important outcome in patients with ACS and in those undergoing emergent percutaneous coronary intervention (PCI).[12]

For these reasons, we genotyped the subjects with acute coronary syndromes, to evaluate the impact of non-genetic factors and polymorphisms in ABCB1, Cytochrome P450 genes on platelet response to clopidogrel. Understanding the prevalence of drug metabolism related genetic polymorphisms will enhance clinical understanding of racial differences in drug reaction, contributing to the development of personalized medicine in Morocco.

Methods

Study Population

This prospective study analyzed clinical, paraclinical, and pharmacogenetic data from patients with acute coronary syndromes treated with clopidogrel at 300 mg loading dose in 55 patients during the period of May 2016 to February 2017 at Hassan II University Hospital (Fez, Morocco).

We included patients diagnosed with their first ACS: patients presenting NSTEMI, and patients with STEMI admitted 12 hours after shiest Paine on set. Cases excluded were patients with incomplete data and patients with STEMI who benefit from revascularization using fibrinolysis or primary angioplasty, because of the emergency revascularization of these patients. The study protocol was approved by the Ethics Committee of the Faculty of Medicine and Pharmacy, University Hospital Hassan II, Fez, Morocco, and was consistent with the principles of the Declaration of Helsinki. A written informed consent was obtained from all participants.

Assessment of Antiplatelet Response

The antiplatelet response was established with the VerifyNow $P2Y_{12}$ Test for Clopidogrel (Accumetrics, Inc., San Diego, CA, USA), which measures ADP-induced aggregation (the degree of platelet aggregation in the presence of $P2Y_{12}$ inhibitors).[13,14] The level of the platelet $P2Y_{12}$ receptor blockade was expressed as $P2Y_{12}$ Reaction Unit (PRU). The platelet reactivity test was performed 8 hours after 300 mg loading dose administration. According to the VerifyNow reference guide, patients with PRU below 208 were considered as responders and over 208 PRU as non-responders to the clopidogrel loading dose.

Genotyping

The whole blood genomic DNA was extracted using DNA extraction kit (QIAamp DNA Mini Kit, QIAGEN GmbH) following the manufacturer's instructions. The samples were genotyped using the GenoChip CYP+ array (PharmGenomics GmbH, Mainz, Germany) to test for 13 variant alleles of Cytochrome P450 2C9, 2C19, 3A4, 3A5, 1A2, and 2B6 genes (Table 1).

DNA amplification was performed using five separate PCR mixes (A-E) according to PCR protocol supplied with GenoChip CYP+ protocol version 1.4 (April 2018). An aliquot of 60 µL of the denaturalizing mixture (ROM) and 2 µL of each PCR product (A-E) was transferred to a single reaction tube and denatured at 95°C for 2 minutes. Afterwards, the

Table 1 Alleles and Variations Detected by the GenoChip CYP+ Array

Genes	Allele	Variation	rs Number
CYP1A2	*1C	−3860G>A	rs2069514
	*1F	−163C>A	rs762551
CYP2B6	*6	516G>T	rs3745274
	*6	785A>G	rs2279343
CYP2C9	*2	430C>T	rs1799853
	*3	1075A>C	rs1057910
CYP2C19	*2	430C>T	rs4244285
	*3	1075A>C	rs4986893
	*17	−806C>T	rs12248560
CYP3A4	*1B	−392A>G	rs2740574
	*22	15389C>T	rs35599367
CYP3A5	*2	27289C>A	rs28365085
	*3	6986A>G	rs776746

hybridization buffer was immediately added and subsequently transferred to array tubes, where the denatured DNA binds to the oligonucleotide probes immobilized on the Array Chip. In the conjugation step, the streptavidin-horseradish peroxidase complex is bound to the biotinylated targets. Then the precipitation is formed by the cleavage of the tetramethylbenzidine substrate into a colored pattern. Finally, the resulting patterns are detected by a CCD-based reader and analyzed with the software provided by the manufacturer.

For sanger sequencing: The ABCB1genomic sequence was obtained from the NCBI data base (http://www.ncbi.nlm.nih.gov). The PCR primers of ABCB1 C3435T were designed by Primer 5.0 software: forward primer 5'-AAGTGTGCTGG TCCTGAAGTT-3' reverse primer 5'-AAGGGTGTGATTTGGTTGC-3'. The PCR reaction contained 15.8μL nuclease-free water,5μLDreamTaq Green Buffer (includes 20 mM MgCl2), 1 μL dNTP (0.3 mM), 0.2 μLDreamTaq DNA Polymerase (5 U/μL),1 μL of each primer (10 μM) and 1 μL DNA (100 ng/μL). The final volume of the PCR reactions was set to 25 ultot. PCR reactions were performed using the ProFlex PCR System (Applied Biosystems, Forest City, CA, USA) in the following optimized conditions: initial denaturing at 94 °C for 3 min, followed by 35 cycles: denaturation at 94 °C for 30 sec, annealing at 60 °C for 30 secs, elongation at 72 °C for 60 secs, and final extension at 72 °C for 9 min. The PCR products were then sequenced using BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems, CA, USA) and 1 μL for primer (1 μM) in 10 μL final volume per reaction. The sequencing products were sequenced using a 3500Dx Series Genetic Analyzer (Applied Biosystems).

Phenotyping

According to the literature and with the use of the Clinical Pharmacogenetics Implementation Consortium, the CYPs genotypes were classified by their known effect on enzymatic function (gain-of-function allele, or loss-of-function).[15,16]

CYP1A2 *1C, *1, and *1F were assigned activity scores of 0.5, 1, and 1.5, respectively. Patients with CYP1A2 *1F/*1F genotype were assigned a UM phenotype. Moreover, patients with CYP1A2 *1/*1F and *1C/*1F genotypes were categorized as having a CYP1A2 Normal Metabolizer/Rapid Metabolizer (NM/RM) phenotype. CYP1A2 *1C/*1C genotype was classified as PM.[17]

It has been documented that CYP2B6*6A allele (c.516G>T, c.785A>G),[18] alter substrate binding and/or catalytic activity,[19] and decrease response to clopidogrel.[20] Therefore, CYP2B6*6A genotypes were classified as PM (carriers of 2 mutations or 1 mutation in homozygosis), IM (carriers of CYP2B6*6A in heterozygosis), and NM (carriers of the *1/*1 genotype).

Moreover, CYP2C9 genotypes were also classified as PM (carriers of 2 mutated alleles), IM (carriers of *2 or *3 in heterozygosis), and NM (carriers of the *1/*1 genotype).[21,22]

For CYP2C19 genotypes were divided into three groups; NM (*1/*1), IM-PM (*1/*2, *2/*2, and *2/ *17), and UM (*1/*17 and *17/*17). CYP2C9 genotypes was also classified as NM (*1/*1), IM-PM (*1/*2, *1/*3, *2/*2 and *2/*3).[15]

Additionally, patients with CYP3A4 *1/*1 were classified as NM, and patients carrying the CYP3A4 *1/*22 and *22/*22 genotypes were classified as IM-PM.[10] Patients with CYP3A5 *1/*3 genotype were classified as expressers and patients carrying CYP3A5 *3/*3 genotype, as non-expressers.[15] Finally, CYP3A4*1B (−392A>G) genotype, no strong evidence of the effect of the mutation was described in the literature.

Statistical Analysis

Statistical analysis was performed using SPSS software version 21. (SPSS Inc, Chicago, Il, USA). Associations between Genotype or Phenotype distribution and clopidogrel response were assessed using the chi-square or Fisher's exact tests, differences in quantitative parameters between individuals were analyzed using one-way analysis of variance (ANOVA). P-values <0.05 was considered a statistically significant.

Results

Patient Characteristics

The baseline characteristics of the study population were summarized in Table 2. For all the 55 patients enrolled, the average age was 58.47±8.67 years. The youngest patient was 31 years old, while the oldest was 73 years old. 76.4% were males, 73% presented with non-ST-elevation myocardial infarction, and 27% presented with ST-elevation myocardial infarction, the most frequent risk factor was smoking 34 patients (61.8%), diabetes mellitus 20 patients (36.6%), hypertension 14 patients (25,5%).

The patients were treated with enoxaparin (89.1%), statins (94.5%), beta-blockers (47.3%), AEC inhibitor (38.2%), proton pump inhibitors (14.5). All the patients were treated with acetylsalicylic acid.

Table 2 Baseline Characteristics of Patients

Characteristic	Total (n = 55)	Clopidogrel Responder (n = 36)	Clopidogrel Non-Responder (n = 19)	*P*_value
Age, yrs	58.47±8.67	57.5±9.3	60.4±7.1	0.2
Men. N (%)	42 (76.4)	30 (83.3)	12 (63.2)	0.1
Body Weight, kg	72.24±12.16	72.03±12.98	72.52±11.20	0.9
Umbilical waist, Cm	94.87±14.52	94.03±12.83	96.04±16.83	0.6
BMI, kg/m2	26.49±4.6	26.25±4.5	26.95±4.9	0.6
Cardiovascular risk factors, n (%)				
Diabetes mellitus	21 (38.2)	11 (30.6)	10 (52.6)	0.1
Hypertension	14 (25.5)	8 (22.2)	6 (31.6)	0.6
Smoking	34 (61.8)	23 (63.9)	11 (57.9)	1
Dyslipidemia	5 (9.1)	3 (8.3)	2 (10.5)	1
Platelets, $10^3/\mu L$	233.109±70.382	230.750±62.120	237.579±85.579	0.7
STEMI, n (%)	15 (27.3)	12 (80)	3 (20)	0.042
GRACE score	124.22±32.98	125.9±34.7	121.1±30.2	0.6
In-hospital treatment, n (%)				
Enoxaparin	49 (89.1)	32 (88.9)	17 (89.5)	1
Statin	52 (94.5)	34 (94.4)	18 (94.7)	1
PPI	8 (14.5)	4 (11.1)	4 (21.1)	0.4
AEC inhibitor	21 (38.2)	14 (38.9)	7 (36.8)	0.9
Beta blocker	26 (47.3)	16 (44.4)	10 (52.6)	0.5

Abbreviations: BMI, body mass index; STEMI, ST-elevation myocardial infarction; PPI, proton pump inhibitors; AEC inhibitor, angiotensin-converting enzyme inhibitor.

Patients were subdivided into clopidogrel responder (PRU≤208) and clopidogrel non-responder group (PRU>208), 19 patients (34.55%) were clopidogrel non-responders, whereas 36 patients (65.45%) were clopidogrel responders. Patient characteristics distribution in these two groups, demographic data, cardiovascular risk factors, and in-hospital treatment GRACE score were similar in both groups (all P>0.05).

Genotype Results of the Studied CYP450 and ABCB1 C3435T Variants

In this study, thirteen genetic variants in CYPs were investigated, including CYP1A2*1F, *1C; CYP2B6*6A (516G>T, 785A>G); CYP2C9*2, *3; CYP2C19*2, *3, *17; CYP3A4*1B, *22; CYP3A5*2, *3. The tested alleles CYP2C9*3, Cyp2C19*2, Cyp2C19*3, CYP3A4*22, and CYP3A5*2 were not found in our study population, which allows nine alleles to be analyzed. The distribution of the studied genetic polymorphisms is shown in Table 1.

Interestingly, the CYP3A5*3 variant was detected in all patients, *1/*3 heterozygote genotype in 15 patients (27.3%), and the homozygote genotype *3/*3 in 40 patients (72.7%). The majority of patients had at least one mutation in CYP1A2 gene, in which 24 patients (43.6%) had *1/*1F, 14 (25.5%) with *1F/*1F and, 11 (20%) with *1C/*1Fgenotype. 15 subjects carrying *1/*17 genotype in CYP2C19 gene (27.3% of the study population). In the CYP2B6 gene, (516G>T) heterozygote mutation was detected in 20 cases (36.4%), the (785A>G) AG genotype was found in 20 cases (36.4%). For CYP3A4, the presence of the *1B allele accounted for 34.5% of the subjects. The CYP2C9*2 variant was observed only in 6 patients (10.9%). Among ABCB1 C3435T variant, 21 (38.2%), 29 (52.7%) and 5(9.1%) patients had wild type (CC), heterozygote (CT) and TT genotypes, respectively (Table 3). Due to the low

Table 3 Distribution of Genotype and Allele Prevalence in the Study Population

Genotype SNP	Population n=55 No (%)
CYP1A2	
*1/*1	6(10.9%)
*1/*1F	24(43.6%)
*1F/*1F	14(25.5%)
*1C/*1F	11(20%)
CYP2B6 (516G>T)	
GG	35(63.6%)
GT	20(36.4%)
CYP2B6 (785A>G)	
AA	35(63.6%)
AG	20(36.4%)
CYP2C9	
*1/*1	49(89.1%)
*1/*2	6(10.9%)
CYP2C19	
*1/*1	40(72.7%)
*1/*17	15(27.3%)
CYP3A4	
*1/*1	36(65.5%)
*1/*1B	19(34.5%)
CYP3A5	
*1/*3	15(27.3%)
*3/*3	40(72.7%)
ABCB1 C3435T	
CC	21(38.2%)
CT	29(52.7%)
TT	5(9.1%)

Table 4 Genotype/ Phenotype Distribution of the Studied Genes According to Clopidogrel Responder and Non-Responder Groups

Gene	Genotype/Phenotype	Clopidogrel Responder n=36 No (%)	Clopidogrel Non-Responder n=19 No (%)	P value
ABCB1 C3435T				0.057
	WT (n = 21)	17 (47.2%)	4 (21.1%)	
	T carriers (n = 34)	19 (52.8%)	15 (78.9%)	
CYP1A2				1
	NM/RM (n = 41)	27 (75%)	14 (73.7%)	
	UM (n = 14)	9 (25%)	5 (26.3%)	
CYP2B6				0.8
	IM/NM (n = 42)	28 (77.8%)	14 (73.7%)	
	PM (n = 13)	8 (22.2%)	5(26.3%)	
CYP2C9				1
	NM (n = 49)	32 (88.9%)	17 (89.5%)	
	IM (n = 6)	4 (11.1%)	2 (10.5%)	
CYP2C19				1
	NM (n = 40)	26 (72.2%)	14 (73.7%)	
	UM (n = 15)	10 (27.8%)	5 (26.3%)	
CYP3A4*1B (−392A>G)				0.4
	AA (n = 36)	25 (69.4%)	11 (57.9%)	
	AG (n = 19)	11 (30.6%)	8 (42.1%)	
CYP3A5				0.9
	Expressers (n = 15)	9 (28.1%)	5 (26.3%)	
	Non-expressers (n = 40)	23 (71.9%)	14 (73.7%)	

Note: Patients with aggregation >208 PRU were considered as clopidogrel non-responders.
Abbreviations: IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer; WT, wild type.

frequency of TT genotype subjects, statistical analysis was done between wild-type subjects and T allele carriers (CT heterozygote and TT homozygote).

Relationship Between CYP450 and ABCB1 C3435T Genotypes and Clopidogrel Responses

In the present study, we investigated the effects of variants in CYPs and ABCB1 genes on patients response to clopidogrel 300 mg loading dose. Genotype distributions of CYPs and ABCB1 among clopidogrel responses are shown in Table 4. As previously described, the CYPs genotypic classification was used; CYP1A2 (NM/RM, UM), CYP2B6*6A (NM/IM, PM), CYP2C9 (NM, IM), CYP2C19 (NM, UM), CYP3A5 (Expressers, Non-expressers).

Genotype distribution of the ABCB1 C3435T variant was marginally significant between the two groups of patients (P = 0.057), the frequency of the T allele in Clopidogrel non-responders was higher than in the responders (15/19; 78.9%) and (19/36; 52.8%) respectively. However, there was no influence of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, or CYP3A5 on the clopidogrel response (all P>0.05) (Table 4).

Discussion

In this study, we enrolled fifty-five ACS patients who received clopidogrel 300 mg loading dose and associated CYP SNPs, ABCB1 C3435T variant, and non-genetic factors with clopidogrel response. Based on the VerifyNow test, our results revealed that 34.5% of ACS patients were clopidogrel non-responders. This percentage was slightly lower than previous studies. Saiz-Rodríguez et al, found that 44% of patients were non-responders to clopidogrel, considering that a value over 180 PRU is predictive of no drug effect.[10] In another study conducted by Yi et al, in which another method,

light transmittance aggregometry, was used to measure platelet aggregation, and they found that 40% of patients treated with clopidogrel were non-responders.[23]

The variability in response to clopidogrel is a well-known problem since an average of 4% to 30% of patients have an inadequate antiplatelet response. Several studies have reported this effect following the administration of the clopidogrel loading dose.[17–24] Factors such as; age, comorbidities, concomitant treatments, and body mass index, may explain less than 10% of this response variability.[5–25] In this study population, demographic characteristics (age, Body Weight, Umbilical waist, body mass index), comorbidities (diabetes mellitus, lipid profile, hypertension, smoking) concomitant treatments (enoxaparin, statin, PPI, AEC inhibitor beta-blocker) were not associated with clopidogrel response. Therefore, pharmacogenetics could be of great importance.

Previous studies suggested an association of clopidogrel response with gene polymorphism involvement in clopidogrel metabolism and absorption.[20–27] Therefore, this study investigated the relationship between cytochrome P450 variants in CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, ABCB1, and clopidogrel response. Our data revealed that CYPs genotypes were not associated with clopidogrel response.

These results were not in line with Mega et al,[3] in a sub-study of TRITON-TIMI 38, which showed that the response to clopidogrel loading dose has been influenced by genetic variants in the CYP2C19. In this study, CYP1A2 and CYP2C9 were not associated with a difference in clopidogrel response. These results are in accordance with a recent study of Saiz-Rodríguez, in which the CYP1A2 and CYP2C9 alleles did not affect clopidogrel pharmacodynamics in a Spanish population.[10]

In this series of patients, despite the high frequency of CYP3A5 non-expressors in our series of patients, the CYP3A5*3 genotypes did not significantly affect the response to clopidogrel. Similar results were observed in a study conducted by Holmberg et al study, in which the CYP3A5*3 allele did not affect clopidogrel pharmacodynamics in healthy volunteers after a 600 mg loading dose.[28] However, another study suggested that the role of CYP3A5 in the metabolism of clopidogrel is more relevant than previously cited.[29] In this context, Yi et al showed a significant association between CYP3A5*3 genotypes and the antiplatelet effect of clopidogrel after one week of clopidogrel maintenance dose.[23]

Clopidogrel absorption is mainly limited by the efflux transporter P-glycoprotein which is encoded by ABCB1 gene. After oral administration, The P-glycoprotein transporter located in the intestinal epithelial cell wall expels the clopidogrel into the intestinal lumen. Several studies demonstrated that ABCB1 C3435T was associated with lower levels of plasma clopidogrel and its active metabolite (2-oxo-clopidogrel). Carriers of the ABCB1 3435 TT genotype have reduced platelet inhibition and are at increased risk of recurrent ischemic events during clopidogrel treatment.[3–7]

Regarding the role of ABCB1 C3435T on clopidogrel response, 78.9% of T carriers showed non-response to clopidogrel. The C3435T variant was closely associated with non-response to clopidogrel after 300 mg loading doses. A Moroccan study has shown that 62.5% of the non-responder group were carrying the mutant allele.[30] These results are similar to those of Namazi et al, who investigated the clopidogrel response 2 hrs after 600 mg loading dose administration. They found a tendency to increase platelet inhibition by wild-types compared to the T variant group.[24] However, a multicenter study reported a significant association in which TT homozygote carriers had less platelet inhibition after a loading dose of clopidogrel.[3] Moreover, Stokanovic et al, reported in a pharmacokinetic study that when treated with clopidogrel loading doses of 300 or 600 mg, individuals with TT homozygous genotype have reduced concentrations of clopidogrel and active metabolite.[7] In a study where they investigated the influence of the increased loading dose from 300 mg to 600 mg according to platelet reactivity monitoring, Wang et al suggested that increased and adjusted clopidogrel loading dose attenuated clopidogrel resistance in ABCB1 3435T carriers.[31]

We did not measure the level of plasma clopidogrel nor its active metabolite in this investigation. In this pharmacogenetic study, patients treated with clopidogrel received a 300 mg loading dose; We are unable to comment on the impact of ABCB1 C3435T variation in patients taking different doses. Due to a limited sample size, there is a chance that the current study will be biased, which may explain the absence of CYP2C19*2, *3 variants.

In summary, no significant difference was found between the investigated polymorphisms and the response to clopidogrel, except for the marginal signification of the ABCB1 3435T variant, despite the small sample size, the present study demonstrates that patients with ABCB1 3435T variant were more likely non-responders to clopidogrel. This should be considered as a predictive factor for clopidogrel response, to distinguish responder patients from those likely to be non-responders.

For patients with reduced clopidogrel antiplatelet effects, increasing clopidogrel dosage or switching to other medicines such as ticagrelor or prasugrel may be considered. In the future, large multi-centric randomized, and well controlled trials with a large number of patients, are needed to obtain significant and definite conclusions.

Disclosure

The authors report no conflicts of interest in this work.

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