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Research Article

Relevance of genetic polymorphisms of the human cytochrome P450 3A4 in rivaroxaban-treated patients

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A B S T R A C T

Rivaroxaban is an anticoagulant drug that prevents forming of blood clots. In addition, it can be administered to prevent and treat thrombotic diseases such as atrial fibrillation, cardiac arrhythmia, heart valve disease, orthopedic surgery, and thrombophilia to reduce the risk of thrombosis. Various factors such as age, gender, diet, medications, and genetic factors effectively determine the dose of rivaroxaban. Genetic variability in drug-metabolizing enzymes, including the cytochrome P450 (CYP450) enzymes and especially CYP3A4, has been associated with rivaroxaban response. The current study aimed to identify the frequency of CYP3A4 common polymorphisms, as well as their association with rivaroxaban response in 100 patients of Arab descent (48.6% female). CYP3A4 gene polymorphisms were examined by the PCR-RFLP method, and the findings were analyzed by SPSS 16 software and t-test. The frequency of CYP3A4*1B/*1B, CYP3A4*1B/*1A, CYP3A4*1B/*1C, and CYP3A4*1A/*1C was 67.35%, 10.64%, 19.12% and 2.89%, respectively. According to our results, CYP3A4 *1B/*1B genotype was the most common, and patients with CYP3A4*1B/*1B alleles needed a higher daily dose of rivaroxaban than *1B/*1A, *1B/*1C, and *1A/*1C carriers (9.57 ± 1.54 mg/day, P=0.015). Therefore, according to the results, CYP3A4 gene polymorphism has an important effect on the dose of rivaroxaban required to maintain the International Normalized Ratio (INR) in the range of 2-3.

1. Introduction

Rivaroxaban is an anticoagulant drug that prevents blood clots from forming [1]. In addition, it can be administered to prevent and treat thrombotic diseases such as atrial fibrillation, cardiac arrhythmia, heart valve disease, orthopedic surgery, and thrombophilia to reduce the risk of thrombosis [2]. Given that excessive doses can lead to severe bleeding and underdosing can lead to life-threatening thrombosis, it is crucial to identify and prescribe the right dose of rivaroxaban for each patient, based on his genetic background [3]. Studies have shown that about 1% of patients receiving rivaroxaban suffer from severe bleeding and death [4; 5]. In addition, following the use of rivaroxaban in 15% of patients, bleeding occurs with milder degrees [6].

Nowadays, the Prothrombin Time - International Normalized Ratio (PT-INR) test is used to adjust the dose of rivaroxaban. This test is necessary to minimize rivaroxaban's side effects, achieve the best therapeutic dose, and maintain the International Normalized Ratio (INR) in the range of 2 to 3 thrombotic

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diseases [7]. According to most guidelines, achieving the target INR, especially in the first weeks of treatment, requires doses of about 5 mg per day (an amount close to the maintenance dose). Physicians adjust to the patient's required dose by measuring alternating PT-INR [8]. Various studies have shown that administering a fixed amount of rivaroxaban to start treatment leads to drug poisoning in a group of patients and causes fatal bleeding complications, especially in the first weeks of treatment [9; 10]. Further studies have shown that in addition to age, sex, weight, mobility, and diet of the patient, genetic characteristics (gene polymorphisms) also play a decisive role in the patient's response to medication [11; 12].

Rivaroxaban is a racemic mixture consisting of two R and S enantiomers [13]. The S-enantiomer of rivaroxaban is 3 to 5 times more potent in inhibiting vitamin K than the R-enantiomer, and this enantiomer is considered an undesired compound [14]. However, the elimination of S-enantiomer from the body is three times faster than R-enantiomer. The cytochrome P450 3A4 is the major enzyme involved in the metabolism of rivaroxaban S-enantiomer, and approximately 40% of a dose is eliminated unchanged by the kidneys [15; 16]. The CYP3A4 gene is located on chromosome 7 (long arm of q22.1), which its alleles are known as CYP3A4*1.001 (formerly *1B) in normal individuals [17; 18]. CYP3A4 is 34,205 bp long and has 13 exons with a 1,512bp coding region [19]. A 1,512-bp coding region produces an enzyme of 504 amino acids called cytochrome P450 3A4 [20]. Under the activity of this enzyme, the S-enantiomer of rivaroxaban is converted to its inactive metabolites, thereby reducing its plasma levels [21]. Several polymorphisms of the CYP3A4 significantly affect the activity of rivaroxaban [22]. Variation in the CYP3A4 gene is significant in white people (13% - 18%), while it is rarely seen in people of Asian and African descent [23; 24].

In the 392 locus polymorphism, adenine replaces guanine (AF280107.01, -392A>G) and is known as the CYP3A4*1.002 allele (formerly *1A). This nucleotide shift replaces arginine with cysteine and produces a protein with enzymatic activity reduction. The activity of this protein is reduced by 20% compared to its wild type in the heterozygous state. In the homozygous state, its protein activity is reduced by 50% compared to its wild type. [25-27].

In the 444 locus polymorphism, guanine replaces thymine (-444T> G) and is known as the CYP3A4*1C allele. As a result of this replacement, the amino acid leucine replaces the amino acid isoleucine at locus 444. The latter protein has minimal enzymatic activity, reducing its activity by 10% compared to its wild type in the heterozygous state. The frequency of this allele in white people is 6% - 10%. For a person with CYP3A4*1C and CYP3A4*1A alleles (heterozygous), the daily dose of rivaroxaban should be reduced to 25% compared to a person with the wild alleles. As a result, people with the *1A/*1C alleles have more bleeding complications than the *1B allele, and a reduced dose of rivaroxaban is needed than the *1B allele [25; 28].

Also, for a carrier of *1A and *1C alleles simultaneously, the required dose of rivaroxaban is much lower than the homozygotes of these alleles [29]. Based on these polymorphisms, patients were divided into three groups: normal (CYP3A4*1B), slow (CYP3A4*1A), and very slow (CYP3A4*1C) metabolizers [30; 31]. The rivaroxaban levels in the blood of slowly and very slowly metabolizing patients are higher than normal patients with the same usual dose, so they are prone to bleeding of varying severity, which may be dangerous or even fatal [32]. Compared with other foreign compound metabolizing enzymes in the human body, Cytochrome P450 3A4 (CYP3A4) is involved in more clinical drug metabolism. Recently, more and more evidence has shown that mutations in the CYP3A4 gene are functionally significant. In rare cases can lead to loss of activity, which means enormous consequences for patients [17]. Although several studies have been performed on rivaroxaban and CYP3A4 genotypes in different parts of the world [25; 28; 33] no sufficient published data have been performed on the role of CYP3A4 in rivaroxaban on Middle East people, especially Arab origins. Therefore, the initial aim of the

current study was to identify the frequency of CYP3A4 alleles in patients of Arab origin from the Middle East. In addition, the study aims to investigate associations between the metabolizing status of CYP3A4 and response to rivaroxaban, in terms of efficacy and toxicity.

2. Materials and methods

2.1 Study participants

This experimental study was performed on 100 patients of Arab origin from the Middle East. Patients' recruitment took place at the Alhollol Private Hospital, from 2018 to 2019. The inclusion criteria, included the age of patients older than 18 years, being Arab of the Middle East for at least two generations, being unrelated to other patients, able to provide written informed consent and administration of rivaroxaban for 1st time. Exclusion criteria were as follows: The study was approved by the National Committee for Ethics in Biomedical Research and all patients were informed about the study aim and provided their written informed consent. Five patients were excluded from the study due to insufficient information about their demographic and clinical records. At the beginning of admission to the hospital, the study questionnaire was completed. In this questionnaire, the clinical and demographical data of each patient was recorded. The mean age of patients was 62.7 years (34 to 85 years). 48.6% of patients were female and 51.4% were male. The average weight in this group was 67.9 kg (45 to 117 kg). Patients took rivaroxaban for a variety of reasons (15% due to high blood pressure, 13% due to cardiac arrhythmia, 3% due to atrial fibrosis, 16% due to hypertension and myocardial infarction, 27% due to heart valve replacement, and 26% due to other heart problems). All the demographic and clinical data at the baseline for the included patients are shown in Table 1. 5ml of peripheral blood (EDTA-K2 anticoagulant) was collected and transferred to the laboratory. Buffy coat was separated, and DNA was extracted using HigherPurity™ Blood DNA Extraction Kit (Canvax Biotecha) according to the manufacturer's instructions. The integrity DNA was qualitatively tested by the polymerase chain reaction (PCR) method for the beta-globin gene [34].

2.2 Genotyping of CYP3A4 alleles

Genotyping of CYP3A4*1A and CYP3A4*1C was performed using the restriction fragment length polymorphism technique (RFLP-PCR). PCR products were digested with 10 units of *SmaI* endonuclease enzyme for CYP3A4*1A, 10 units of *RsalI* for CYP3A4*1B, and *HphI* endonuclease enzyme and CYP3A4*1C at 37°C, overnight. DNA fragments were visualized through 2.5% Agarose gel (Table 1).

Table 1. Enzymatic digestion of PCR products

Enzyme	Restriction endonuclease	DNA fragments (bp) digested		
		The Most frequent	Heterozygous	Homozygous
CYP3A4 *1A	*SmaI*	120, 49	169, 120, 49	169
CYP3A4 *1B	*RsalI*	217, 70	287, 217, 70	287
CYP3A4 *1C	*HphI*	287	287, 187, 100	187, 100

PCR was performed with a final volume of 25µl containing 100 ng of DNA, 1µl of each primer, 2.5µl of X10 buffer, 2.5µl of $MgCl_2$, 0.5µl of DNTP and 1 unit of Taq-polymerase enzyme (Table 2).

Table 2. Conditions for performing polymerase chain reaction

Repeat	Time	Temperature (°C)
1 cycle	5 min	95
	30 sec	95
25 cycles	30 sec	51-55
	20 sec	72
1 cycle	8 min	72

CYP3A4*1A, CYP3A4*1B, and CYP3A4*1C were amplified using the primers that are listed in Table 3. All primers were designed according to the Rs Number of the SNP.

Table 3. Primers sequences and expected product size for CYP3A4*1A, CYP3A4*1B, CYP3A4*1C PCR amplification

Gene	Sequence	Rs Number	Product Size (bp)
CYP3A4*1A	F(5´-AAGTCCTCAGAATCCACAGCG-3´) R(5´-CACACAGCAAGAGTCTCACAC-3´)	776746	416
CYP3A4*1B	F(5´-ATCTGTGTGAGGAGTTTGGT-3´) R(5´-GTGAGGCTGTTGGATTGTTT-3´)	2740572	470
CYP3A4*1C	F(5'-TCAGAGCCTTCCTACATAGAG-3') R(5'-GTCTTTCCTCTCCTTTCAGC-3')	2242480	315

2.3 Statistical analysis

To evaluate the association between the genotypes CYP3A4*1B*1B, CYP3A4*1B*1A, CYP3A4*1B*1C, and CYP3A4*1A*1C and treatment response, were performed T-test, using the SPSS 16 software. Hardy–Weinberg Equilibrium (HWE) was calculated using the simple χ^2 goodness-of-fit test.

3. Results

This study was performed on 95 patients taking rivaroxaban who were eligible for the study. The mean age of patients was 62.7 years (34 to 85 years). 48.6% of patients were female, and 51.4% were male. The average weight in this group was 67.9 kg (45 to 117 kg). Patients took rivaroxaban for a variety of reasons (15% due to high blood pressure, 13% due to cardiac arrhythmia, 3% due to atrial fibrosis, 16% due to hypertension and myocardial infarction, 27% due to heart valve replacement, and 26% due to other heart problems). According to this study, age had no significant effect on the dose of rivaroxaban.

In studied patients, the frequency of individuals with *1B/*1B, *1B/*1A, *1B/*1C, and *1A/*1C alleles for CYP3A4 gene was 67.35%, 10.64%, 19.12% and 2.89%, respectively (Fig. 1).

Using SPSS 16 software, the mean of rivaroxaban consumption in individuals with CYP3A4 genotype was determined (Table 4). The dose of rivaroxaban used in patients with *1B/*1B and *1B/*1A alleles are higher than patients with *1B/*1C allele.

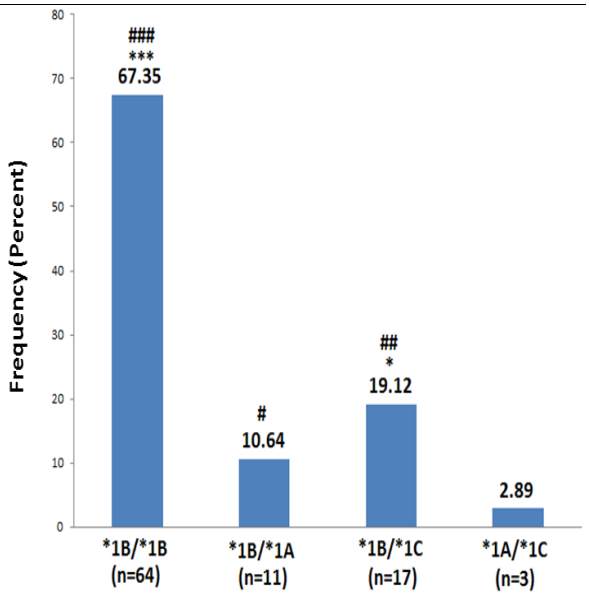

Fig. 1. Frequency of CYP3A4 gene alleles in the studied patients; * means P<0.05, *** means P<0.001, # means P<0.05 in comparison with *1A/*1C, ## means P<0.01 in comparison with *1A/*1C, ### means P<0.001 in comparison with *1A/*1C

Table 4. Mean of rivaroxaban consumption in patients with CYP3A4 genotype

CYP3A4 Genotype	The Dose of Rivaroxaban (mg/day)	Mean INR
*1B/*1B	9.57 ± 1.54	2.26
*1B/*1A	6.93 ± 1.39	2.47
*1B/*1C	6.29 ± 1.31	2.52
*1A/*1C	5.62 ± 1.02	2.49

4. Discussion

Rivaroxaban is one of the most commonly used drugs to prevent and treat thrombotic diseases [1]. Annually, many patients are candidates for received rivaroxaban for reasons such as atrial fibrillation, cardiac arrhythmia, heart valve disease, thrombophilia, and so on [35].

Just as taking the correct dose of rivaroxaban can be helpful, taking the wrong dose can also have side effects [36]. Therefore, determining the appropriate dose and

monitoring it and finding influential risk factors for each patient was very important. Although age, sex, weight, medical history, and some medications are essential factors in the dose required for rivaroxaban, genetics' role is crucial today [37].

At present, in many medical centers, molecular studies of the CYP3A4 gene are used as a biomarker to prescribe the appropriate dose of rivaroxaban and reduce the time to reach the target dose and thus reduce the side effects of the drug [38]. This method reduces the length of time that patients are hospitalized and thus reduces the cost of the treatment [39].

The present study evaluated three CYP3A4 alleles. According to this study, the age of patients had no significant effect on the dose of rivaroxaban. The frequency of individuals with *1B/*1B, *1B/*1A, *1B/*1C, and *1A/*1C alleles for CYP3A4 gene was 67.35%, 10.64%, 19.12% and 2.89%, respectively. It showed that the *1B/*1B allele had the highest frequency among patients. In the present study population, *1C allele was more common than *1A, while in 1122 patients, *1A mutant allele was more common than *1C. In fact, 184 of 1122 had the *1A allele [34]. Since the wild allele is the most common allele in different communities and the number of patients in terms of the mutant allele is less than the wild allele, finding the most common mutant allele CYP3A4 requires a larger statistical power.

In this study, it was found that to maintain the INR in the range of 2-3 in patients with *1B *1B and *1B *1A alleles, a higher dose of rivaroxaban is required than those with *1B *1C, and *1A *1C alleles. These results show that CYP3A4 variability can influence rivaroxaban response during the treatment of heart conditions. This finding was consistent with many studies in other populations that showed that the CYP3A4 gene polymorphism reduces the daily dose of rivaroxaban relative to its most frequent allele [40; 41].

5. Conclusion

Rivaroxaban is an anticoagulant drug that prevents thrombosis, and patients can use it to prevent and treat thrombotic diseases such as atrial fibrillation, cardiac arrhythmia, heart valve disease, orthopedic surgery, and thrombophilia to reduce the risk of thrombosis. Since overdose can cause severe bleeding, and under-dose can lead to life-threatening thrombosis, it is essential to determine and prescribe the correct dose of rivaroxaban according to the genetic background of each patient. The aim of the current study was to identify the frequency of CYP3A4 common polymorphisms, as well as their association with rivaroxaban response in 100 patients of Arab descent. The results concluded that the most abundant polymorphism in the study population belonged to *1B/*1B. The CYP3A4 gene genotype was effective in determining the dose of rivaroxaban required by patients. CYP3A4 can be used as a biomarker to determine the dose of rivaroxaban. However, our findings should be replicated in larger-scale studies, before any clinical implications.

Conflict of interest

None of the authors have any conflict of interest to declare.

Consent for publications

All authors approved the final manuscript for publication.

Availability of data and material

The authors have embedded all data in the manuscript.

Authors' contributions

Muhammed Furkan Ercisli designed the idea, helped with doing, and manuscript writing, Gao Lechun helped for doing and helped in sampling and data collection, Sarhang Hasan Azeez helped in sampling and data collection, Rebwar Muhammad Hamasalih helped in sampling and data collection, Siyan Song helped in data analysis, and Zahra Aziziaram helped in study design, sampling, data collection, doing, and article drafting.

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Ethics approval and consent to participate

This study design was approved by ethical code IR.KMU.AH.REC.1396.152 in the research unit. Also, consent forms were completed for all participants.

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