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VKORC1 and CYP2C9 Genetic Variants Coumarin Response in the Mestizo-Mexican Population

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ABSTRACT

Introduction: Polymorphisms in the genetic variations of vitamin K epoxide reductase complex subunit 1 (VKORC1) and Cytochrome P450 subfamily IIC polypeptide 9 (CYP2C9) have been shown to cause variability in anticoagulant response across various ethnic groups. In the Mestizo-Mexican population, with their Amerindian-European and African-Asiatic ancestral origins, the response is expected to differ as well. This study aims to evaluate the anticoagulant response to coumarin in Mestizo-Mexican patients with mechanical heart valve prostheses.

Method: DNA was extracted from blood samples using a commercial genomic DNA purification kit. The polymorphisms rs1799853 CT in the CYP2C9*2 gene and rs9923231VKORC1-G1639A gene were determined using real-time PCR. All patients initially received a dose of 8 mg/day of coumarin, which was adjusted on the second day based on international normalized ratio (INR) levels until reaching a result of 2.5-3.5.

Results : Seventy-six patients with an average age of 58±11 years were undergoing mitral (n=44) and aortic (n=32) valve replacement. Patients carrying GG haplotypes in the rs9923231VKORC1-G1639A gene variant required a significantly higher coumarin dose to reach the therapeutic range compared to those with GA and AA haplotypes (p=0.001). The rs1799853 polymorphism of the CYP2C9*2 A/C gene showed no significant differences between AA, AC, and CC haplotypes (p>0.05).

Conclusion : In the Mestizo-Mexican population, individuals carrying the rs9923231 VKORC1 gene with GG haplotypes exhibited a hyporeactive anticoagulant response compared to those with GA and AA haplotypes, which showed normal and hyperreactive responses, respectively. There were no significant differences in the response of the CYP2C9*2 haplotypes AC carriers.

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Introduction

The coumarin anticoagulant treatment is essential for patients with mechanical cardiac prostheses to reduce the local risk of thrombosis and systemic thromboembolic events. Regular monitoring of anticoagulant coumarin dose is required by measuring the International Normalized Ratio (INR) to maintain anticoagulation within the recommended therapeutic range (2.5-3.5) (1-3). However, in clinical practice, variations in individual anticoagulation response are common, despite good adherence to coumarin doses and a diet free of foods rich in vitamin K. Some authors suggest that this variant response could be due to the presence of specific polymorphisms that result in possible resistance or sensitivity to coumarin anticoagulants (4).

Cytochrome P450 subfamily IIC polypeptide 9 (CYP2C9*2) is the major enzyme responsible for catalyzing the hydroxylation of coumarins, which blocks the synthesis of K-dependent vitamin coagulation factors (II, VII, IX, and X) by inhibiting the gamma-carboxylation of vitamin K (5). Additionally, mutations in the gene encoding the vitamin K epoxide reductase complex subunit 1 (VKORC1) produced in hepatic cells have recently been associated with resistance to coumarin anticoagulant therapy. Polymorphisms or genetic variations in both genomes have shown variable responses to coumarin treatment in different ethnic groups (6-9).

In the Mexican-Mestizo population, variant responses to oral anticoagulants have also been observed, with a significant proportion of patients requiring longer coumarin impregnation times, higher doses, and experiencing difficulty in maintaining an anticoagulant effect within therapeutic ranges. We investigated the response to oral coumarin anticoagulation in Mexican-Mestizo patients with genetic variants rs1799853-CYP2C9*2 AC Haplotypes and rs9923231-VKORC1 GA Haplotypes undergoing cardiac valve replacement with mechanical prostheses.

Materials and Methods

The research which had a cross-sectional prospective study design was approved by the Ethics, Biosecurity, and Research Institutional Committees.

Population Characteristics

Patients with cardiac disease underwent open-heart surgery for valvular replacement in the Cardiovascular Surgery Department, meeting the following criteria**:**

Inclusion criteria: Patients who underwent mitral and aortic replacement with a mechanical prosthesis and signed a consent form.

Exclusion criteria: Patients who underwent mitral or aortic replacement with a biological prosthesis.

Measurements

A 10 ml blood sample was obtained and placed in a sterile tube with EDTA. DNA extraction was performed using the commercial genomic DNA purification kit Prep Mini Spin Kit and a QIAamp DNA Mini Kit from Qiagen. The polymorphisms rs1799853 CYP2C9*2 AC gene and rs9923231 VKORC1 GA gene were determined using Rotor Gene Qiagen real-time PCR. Coumarin impregnation was administered at 8 mg/day on the first day, and the dose was adjusted from the second day according to the INR result until it stabilized between 2.5-3.5. Serum INR levels were determined using CELL-DYN Sapphire (Abbott Lab., Chicago, USA) analyzer. All patients received specific dietary instructions low in vitamin K. From the patients' medical records, age, sex, type of surgery performed, comorbidities, coumarin-interacting drugs, daily and total coumarin dose to achieve a therapeutic range were recorded.

Statistical Analysis

Descriptive analysis was performed using mean, standard deviation, and percentages. Inferential analysis was done with ANOVA and Tukey's post-hoc test. A p-value of < 0.05 was considered significant. IBM-SPSS v29.0 was used for the Operative Windows System.

Results

Seventy-six patients aged 58±11 years who underwent mitral valve replacement (n=44) and aortic valve replacement (n=32) were analyzed. Males accounted for 53% (n=40) and females for 47% (n=36). Comorbidities in all patients included Diabetes Mellitus (26%, n=20), Hypertension (55%, n=42), and Dyslipidemia (45%, n=34). Only 8 patients received drugs with potential interactions with coumarin metabolism (Amiodarone n=12 and carbamazepine n=4) (Table 1). Adherence to treatment and dietary requirements was 100% .

The average coumarin dose required to achieve the recommended anticoagulation range was significantly higher in patients carrying the GG haplotype in the rs9923231VKORC1(G1639A) gene polymorphism compared to the GA and AA haplotypes (p = 0.001). The CYP2C9*2 gene polymorphisms (A1075C) did not show differences between the AA, AC, and CC haplotypes (p > 0.05) (Table 2).

To achieve the recommended therapeutic INR levels, patients carrying the GG haplotype required 3 days, GA haplotype required 2 days, and AA haplotype required 1 day (Table 3). All patients were discharged from the hospital when they achieved an INR level between 2.5-3.5.

Discussion

Long-term anticoagulation is essential for patients undergoing heart valve replacement with mechanical prostheses. The American College of Cardiology, American Heart Association, and European Society of Cardiology recommend, maintaining oral coumarin anticoagulation to achieve an INR level between 2.5-3.5 with level evidence IA (10).

Table 1. Epidemiological Characteristics.

	n	%
Sex		
Male	20	53
Female	18	47
Cardiac Valve		
Mitral	22	58
Aortic	16	42
Comorbidity		
Diabetes Mellitus	10	26
Hypertensión	21	55
Dyslipidemia	17	45
Drug Interactions *		
Amiodarone	6	16
Carbamazepine	2	5

* Drugs with potential interaction in coumarine anticoagulant metabolism.

Table 2. Average weekly coumarin dose and anticoagulation response determined with average INR by genomic variant.

rs9923231VKORC1(1639 G1639A)				
	GG (n=22)	**GA (n=30)**	**AA (n=24)**	**p**
Daily doses (grs)	3.1±0.7	1.7±0.02	1.2±0.03	0.001
Average doses (grs)	22.1±6.1*	12.1±2.6	9.2±2.8	0.001
Average INR	2.03±0.3	2.8±0.2	3.7±0.4	0.001
rs1057910 CYP2C9*2 (A1075C)				
	AA (n=25)	**AC (n=32)**	**CC (n=19)**	**P**
Daily doses (grs)	2±0.2	1.7±0.3	2±0.5	0.86
Average doses (grs)	14.2±6.5	12.1±2.1	14.3±5.5	0.85
Average INR	2.08±0.02	2.8±0.03	3.2±0.5	0.24

INR : International Normalized Ratio;
* Significantly different genotype;
Comparison was made with ANOVA and the p value with Tukey's post-hoc test.

Table 3. Coumarin dosage adjusted to the anticoagulant response according to the genetic variant of the rs9923231VKORC1(G1639A) polymorphism.

	Day 1			Day 2			Day 3		
	INR b	Dosage (mg)	HS	INR	Dosage (mg)	HS	INR	Dosage (mg)	HS
GG (n=22)	1.3±0.2	8	H	1.5±0.2	8	H	2.9±0.5	2-3	H
GA (n=30)	1.4±0.1	8	H	1.9±0.3	4	H	3.2±0.6	1-2	HD
AA (n=24)	1.5±9.1	8	H	2.9±0.4	1-2	HD	3.3±0.5	1-2	OC

INR: Índice Internacional Normalizado; **b:** Basal; **EH:** Hospitalary Estatus; **H:** Hospitalization; **HD:** Hospital Discharge; **OC:** Outpatient Clinic

In clinical practice, the anticoagulant response varies, attributed to poor adherence to diet and interactions with drugs used to treat concomitant conditions. However, in many cases these causes do not fully explain it. In the patients included in this study, poor adherence to a low vitamin K diet was 100%, and only 16 patients were taking drugs that could potentially coumarin interact with coumarins.

Polymorphisms or genetic variations in DNA encoding proteins involved in specific metabolic pathways for coumarins have shown variable interethnic responses due to variations in allelic frequencies of VKORC1 and CYP2C9*2 polymorphisms in Caucasian, Asian, and African populations (11, 12). This variation in the Mestizo-Mexican population could also be different due to their Amerindian-European and African Asian ancestral origins, presenting a challenge in response to oral anticoagulation with coumarins (6, 13-17). Our findings showed that patients carrying the GG haplotype in the rs9923231VKORC1 polymorphism required significantly higher daily and overall doses of coumarin to achieve a therapeutic INR range compared to GA and AA genotypes ($p = 0.001$). Patients with the GG haplotype required at least 3 days of coumarin impregnation and anticoagulant action, needing a higher coumarin dose to maintain it close to the lower limit of the recommended therapeutic range (2.7±0.05), making them hypo responders. Patients with the GA haplotype showed a standard response with a moderate coumarin dose, considered normal responders, while those with the AA haplotype required low doses and were considered hyper-responders, some even requiring only a one-day hospital (6,16, 17).

On the other hand, CYP2C9*2 substrates are weak acidic molecules with a hydrogen bond acceptor that participates in 10 to 20% of known drugs metabolism. Some studies suggest that this interaction could alter the response to coumarin anticoagulants. For example, amiodarone displaces oral anticoagulants from their binding to plasma proteins, increasing the anticoagulant effect, while carbamazepine is an enzyme inducer that increases metabolism and decreases plasma concentrations of oral anticoagulants (18-20). However, the 16 patients who received these drugs showed no differences in AC haplotypes of the rs1057910-CYP2C9*2 polymorphism and did not show differences in anticoagulant response to coumarins ($p > 0.05$) as observes in other ethnic groups.

In summary, this Cohort Study with a pilot sample, shows that in the Mestizo-Mexican population, the response to coumarin anticoagulant in carriers of the rs9923231VKORC1 polymorphism, with the GG haplotype is low and can be considered hypo responders, in contrast to carriers of GA and AA genotypes who are normal responders, and hyper responders, respectively. This suggests that preoperative genotyping could be a screening tool to select the cardiac valve prosthesis with greater strength to offer optimal surgical treatment. This is in line with the guidelines for the management of cardiac valve disease established by the Task Force in 2017, which recommends, with level of evidence IA, implanting biological valve prostheses in patients who are genetically unable to maintain an adequate response to coumarin anticoagulants (10).

Study Limitations/Strengths

Although the sample size is small and may not be conclusive, the results confirm the variability in gene expression in different ethnic groups, even within Latin population of the same country. This variation leads to differences in the response to coumarins,

indicating an area of opportunity where the determination of the s9923231VKORC1 polymorphism expression in the Latin population should be considered prior to coumarin treatment. This is especially important for patients with cardiac disease who will undergo mechanical valve prosthesis implantation.

Conclusion

In the Mestizo-Mexican carriers of the population with polymorphism rs9923231-VKORC1 gene show that the GG haplotype has a hyporeactive anticoagulant response compared to the GA haplotype which has a normal response, and the AA haplotype, which has a hyperreactive response. There are no differences in the response of the CYP2C9*2 haplotypes AC carriers.

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