THE EFFECT OF MAIN GENE POLYMORPHISMS ON STABLE DOSES OF ACENOCOUMAROL IN LONG-TERM ANTICOAGULATION TREATMENT

Abstract nº: DGI-068

E. Jiménez Varo, M. Cañadas Garre, M. Aguilera Gómez, A. Rodriguez, M.A. Calleja Hernández.
Hospital Universitario Virgen de las Nieves, Pharmacogenetic Unit, Granada, Spain.

BACKGROUND

Several variants in CYP2C9 (CYP2C9*2 and especially the CYP2C9*3 allele) and VKORC1 genes (especially the 1639G>A polymorphism) are associated with effective coumarin derivative dose.
The rs2108622 polymorphism in the gene encoding cytochrome P450, family 4, subfamily F, polypeptide 2 (CYP4F2) could also influence warfarin dose with relevant effects on coumarin response.
Concomitant drugs metabolized by CYP450, such as proton pump inhibitors, mainly metabolized by CYP2C19, may increase the risk of overanticoagulation in long-term oral anticoagulation therapy.
Acenocoumarol pharmacokinetics may result altered with the presence of the C3435T gene polymorphism in the P-glycoprotein and has been associated to higher warfarin dose requirements in patients with deep vein thrombosis.

OBJETIVE

Our aim was to evaluate the influence of VKORC1, CYP2C9(CYP2C9*2 and CYP2C9*3 alleles), CYP4F2*2, CYP2C19*17 and MDR1-C3435T gene polymorphisms on the achievement of stable anticoagulation dose in patients treated with acenocoumarol.

MATERIALS AND METHODS

Patients with atrial fibrillation, pulmonary embolism, deep vein thrombosis, metallic aortic valve and metallic mitral valve prosthesis treated with acenocoumarol at a third level hospital were genotyped by Polymerase Chain Reaction (PCR)-Restriction Fragment Length Polymorphism, direct sequencing or real time PCR. Clinical, pharmacological and socio-demographic parameters were analyzed during 6 months of follow-up after starting anticoagulation therapy with acenocoumarol.

RESULTS

One hundred and eighteen patients (mean age:73±12years;55,7%male) treated with acenocoumarol therapy and monitored for dose adjustment were recruited.
The frequency of different genotypes according to stable anticoagulation status is shown in Table 1.
Table 2 shows the frequency of genotypes in stable anticoagulated patients classified by stable anticoagulation dose (High:>28mg/week;Intermediate:7-28mg/week; Low dose:<7mg/week).
The stable anticoagulation status was not associated to any gene polymorphism, and the stable anticoagulation dose was only associated to CYP2C9*3 (0,047).

Table 1. Frequency of different genotypes according to stable anticoagulation status

Gene Polymorphism	Genotype	n	Stable		Total	p-value
			No	Yes		
VKORC1*2 (rs9923231)	CC (WT)	44	30	14	115	0,758
	CT	57	40	17		
	TT	14	11	3		
CYP2C9*2 (rs1799853)	CC (WT)	82	61	21	117	0,223
	CT	33	20	13		
	TT	2	2	0		
CYP2C9*3 (rs1057910)	AA (WT)	98	69	29	116	0,724
	AC	18	14	4		
CYP4F2*3 (rs2108622)	CC (WT)	53	38	15	117	0,352
	CT	50	33	17		
	TT	14	12	2		
CYP2C19*17 (rs12248560)	GG (WT)	85	59	26	113	0,729
	GA	27	20	7		
	AA	1	1	0		
ABCB1 C3435T (rs1045642)	CC (WT)	31	22	9	118	0,864
	CT	56	41	15		
	TT	31	21	10		

VKORC1: Vitamin k epoxide reductase complex,subunit 1; CYP2C9*2: Cytochrome P450 family 2, subfamily C,polypeptide 9, allele variant:2; CYP2C9*3 Cytochrome P450 family 2, subfamily C,polypeptide 9, allele variant: 3; CYP4F2: cytochrome P450, family 4, subfamily F, polypeptide 2; CYP2C19 Cytochrome P450 family 2 subfamily C,polypeptide1 9;ABCB1: ATP-binding cassette, sub-family B, member 1

Table 2. Frequency of genotypes in stable anticoagulated patients classified by stable anticoagulation dose

Gene Polymorphism	Genotype	Stable	Low dose	Intermediate dose	High dose	p-value
VKORC1*2 (rs9923231)	CC (WT)	13	0	13	1	0,280
	CT	17	1	15	1	
	TT	3	1	2	0	
CYP2C9*2 (rs1799853)	CC (WT)	21	1	18	2	0,498
	CT	13	1	12	0	
CYP2C9*3 (rs1057910)	AA (WT)	29	1	27	1	0,047
	AC	4	1	2	1	
CYP4F2*3 (rs2108622)	CC (WT)	15	1	14	0	0,685
	CT	17	1	14	2	
	TT	2	0	2	0	
CYP2C19*17 (rs12248560)	GG (WT)	26	2	22	2	0,542
	GA	7	0	7	0	
ABCB1 C3435T (rs1045642)	CC (WT)	9	1	8	0	0,430
	CT	15	1	12	2	
	TT	10	0	10	0	

(High dose :> 28mg/week; Intermediate dose: 7-28mg/week; Low dose :< 7mg/week)

CONCLUSIONS

The achievement of a stable anticoagulation status is not associated to VKORC1, CYP2C9*2, CYP4F2*2, CYP2C19*17 or MDR1-C3435T gene polymorphisms, although the stable anticoagulation dose is associated to CYP2C9*3.