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

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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.

OBJECTIVE

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 ± 12 years; 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 dose: > 28 mg/week; Intermediate dose: 7-28 mg/week; Low dose: < 7 mg/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).

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.