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Influence of genetic Polymorphisms of Vitamin K Epoxide Reductase Complex Subunit 1 and Cytochrome P450, Family 2, Subfamily C, Polypeptide 9 on the Dose of Phenprocoumon

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Phenprocoumon is used for prevention of thromboembolism. However, it has a narrow therapeutic treatment range and the determination of the required dose is problematic. The single nucleotide polymorphisms (SNPs) of pharmacodynamic factors such as vitamin K epoxide reductase complex subunit 1 (VKORC1) and pharmacokinetic factors like Cytochrome P450 (CYP2C9) can be influence factors of the phenprocoumon dose. The aim of the study was to analyze the influence of SNPs of VKORC1 and CYP2C9 on the steady state weekly dose of phenprocoumon. We hypothesized that polymorphisms of these factors alone or in relation to age, gender, drugs and diseases may influence the steady state weekly dose of phenprocoumon.

The patients who carry CYP2C9*1/*1 and VKORC1 1173CC needed higher weekly dose in comparison to the carriers of CYP2C9*1/*1 and VKORC1 variations (1173CT or 1173TT) (p=0.0016). CYP2C9*1/*1 and VKORC1 1173CC also had higher weekly dose than carriers of CYP2C9 variations (*1/*2, *1/*3 or *2/*2) and VKORC1 variation (1173CT or 1173TT) (p=0.0001).

When SNPs occurred in exon 1 (36G>A, 129C>T), the patients required a higher weekly phenprocoumon dose (22,0mg) than those carrying the wild type (13.9mg) (p=0.0035). When SNPs occurred in exon 3 (358C>T), the patients required a higher weekly dose (26.2mg) than that required by the wild type patients (14.2mg) (p=0.0323)

Beta-receptor antagonists, Calcium channel blockers, Angiotensin-Converting Enzyme inhibitors (p=0.0007) and cardiac drugs (p=0.0595) decreased the dose of phenprocoumon. Coronary heart disease, myocardial infarction (p=0.026), arterial hypertension (p=0.0033), and endocrinal disease (p=0.0161) decreased the dose of phenprocoumon.

VKORC1 polymorphisms are more relevant than CYP2C9 polymorphisms to the weekly phenprocoumon dose. The variations in exon *2* and intron 1 of VKORC1 (1173CT or 1173TT) reduce weekly dose by virtue of pharmacodynamic effects. CYP2C9 variations (*2 or *3) decrease the weekly dose on average. The variations in exon 1 and 3 increase weekly dose. For warfarin, CYP2C9 polymorphisms are more relevant while VKORC1 polymorphisms less relevant for the weekly dose.