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IMPACT OF GENETIC AND NON-GENETIC FACTORS ON WARFARIN RELATED BLEEDINGS IN TURKISH PATIENTS

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BACKGROUND: The CYP2C9 is one of the clinically important drug metabolizing enzymes that demonstrate genetic variations with significant phenotype and clinical outcomes. The patients with CYP2C9*2 and *3 variants need a longer time to reach the warfarin maintenance dose and are at higher risk of serious and life-threatening bleeding. In this study we investigate the impact of the CYP2C9 polymorphisms (*1, *2 and *3) and other personal characteristics on warfarin dose requirements in Turkish patients.

METHODS: A total of 189 unrelated patients with (n=92 cases) and without (n=97 controls) hemorrhagic complications during warfarin therapy was consecutively enrolled. MALDI TOF based Sequenom MassARRAY platform was used for genotyping process. Using multiple statistical analyses different variables were considered separately to assess their impact on warfarin dose adjustment, hemorrhage risk, and its severity.

RESULTS: Determined genotype frequency among all the subjects were 0.69, 0.18, 0.11 for CYP2C9*1*1, 1*2, 1*3, respectively. The cases and the controls did not have a significant difference in terms of wild type (*1*1) and polymorphic variant (*1*2, *1*3) distribution. CYP2C9*1*2 and *1* 3 variants were associated with 12.9% and 17.6% of dose variability. Combined effect of genotype and age on the severity of hemorrhagic complications were analyzed and significant association was determined (p=0.01). Contribution of genotype and age to warfarin dose requirement was defined as 24.4%. The results of logistic regression model showed that aspirin usage during warfarin therapy increases the risk of hemorrhage by <0.2 for therapeutic and >0.2 for supratherapeutic INR range. Gastrointestinal system (GIS) was a common hemorrhage point accounting for 35.8% of the cases, and 72.7% of them had life threatening hemorrhage (p=0.01).

CONCLUSIONS: Present data provides an insight into the common CYP2C9 variants in Turkish patients, clarifying a relationship of genetic background with different personal characteristics and the clinical use of warfarin. Our results will useful to improve algorithms such as initial warfarin dose adjustment and better prediction of anticoagulation response outcomes.