Abstract ID:- 103

Abstract Topic:- Pharmacogenetics

Abstract Title:- Prevalence and genetic association of pharmacogenetic variant of CYP4F2 p.V433M (rs2108622) in Deep vein thrombosis – A south Indian pilot study

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Aims:-Venous thromboembolism (VTE), which includes pulmonary embolism and deep vein thrombosis, is a chronic disease that affects about 10 million individuals annually globally. An increasing number of study findings about the association between the CYP4F2 gene polymorphism and warfarin dose have been published since Caldwell (2008) originally revealed that CYP4F2 gene polymorphisms would alter the warfarin maintenance dose in patients. However, the findings are inconsistent, particularly with regard to south Indian DVT patients. In addition CYP4F2 p.V433M polymorphism known associate with ischemic cardiac disease susceptibility. Thus, the aim of the present study was to investigate the prevalence of CYP4F2 p.V433M polymorphism on warfarin maintenance dose in South Indian DVT patients and investigate the connection between CYP4F2 gene polymorphism and DVT using a case-control study.

Methods:- The polymerase Chain Reaction (PCR)- Restriction Fragment Length Polymorphism (RFLP) was used to genotype CYP4F2 p.V433M polymorphism. The usual $\chi 2$ test or Fisher's exact test were used to evaluate the Hardy-Weinberg equilibrium (HWE). By using χ 2 tests, the genotype frequencies of the cases and controls were compared. The odds ratios (ORs) were used to assess the genotype-specific risks. Statistical significance was established at $P < 0.05$. All statistical analysis were carried out using IBM SPSS (v.22).

Results:- The genotypes of CYP4F2 p.V433M were in HWE. The heterozygous genotype are most commonly observed among case (53.6%) and controls (54.5%) followed by homozygous wild (case- 30%, control – 25.8%) and homozygous mutant (case- 16.4%, control- 19.6%). Thus the according to genotype distribution about 16.4% of DVT possess in higher anticoagulant dosage to achieve the same therapeutic response. Genetic association of CYP4F2 p.V433M revealed no significant difference among the genotypes of case and controls.

Conclusions:- The study showed no association of polymorphism with DVT. Individuals with CYP4F2 variant alleles (433M or “A” allele) have a decreased ability to metabolize vitamin K1, leading to increased amounts of vitamin K1 in the liver. As a result, they need to take greater doses of oral anticoagulants to reach the therapeutic INR. The study warrants further investigation on combination of polymorphism of VKORC1, CYP2C19 and CYP4F2 with the patient’s therapeutic international normalized ratio (INR) to predict the maintenance mean warfarin dose requirement to personalize treatment according patients genetic profile.

Keywords:- Venous thromboembolism ,Deep vein thrombosis, pharmacokinetics, single nucleotide polymorphism