Warfarin Anticoagulant Therapy: Dose Requirement and Ethnic Differences

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Anticoagulant therapy has improved the prognosis of patients with a variety of conditions, including prevention and treatment of venous thrombosis, pulmonary embolism, and thromboembolic complications associated with atrial fibrillation and mechanical prosthetic heart valves.[1] Warfarin is a highly effective and most commonly used oral anticoagulant for more than fifty years. It is coumadin, jantoven generics synthesized by Link ledin 1948. Initially permitted as rodenticide in 1952, and then approved for human use in 1954.[2] It achieves its antithrombotic and anticoagulant effect by inhibiting an enzyme called Vitamin K 2,3-Epoxide Reductase Complex 1 (VKORC1) which is required for reduction of vitamin K 2,3 epoxide to form vitamin K hydroquinone, the active form. This active form is an essential cofactor (with gamma-glutamyl carboxylase) in the post-translational carboxylation of proteins C, protein S and clotting factors II, VII, IX, X.[3] The efficacy of warfarin is based on attaining and maintaining the International Normalized Ratio (INR) of the patient, a measure of clotting capability, within a therapeutic range.[4]

There is great inter-individual variability in the dosage requirement of warfarin to achieve the desired anticoagulation target. Various genetic and environmental factors contribute to this phenomenon. These include body weight, age, vitamin K intake, drug interactions, foods rich in vitamin K and herbs.[5]

Some enzymes in the body metabolizes warfarin, amongst them one major enzyme is encoded by *CYP2C9* gene. The *CYP2C9* gene in humans is located on the chromosome 10 (10q24.2) containing a size of 55 kb across nine exons, which encodes a protein containing 490 amino acids residues. It mainly accounts for 20 % of the entire hepatic cytochrome P450 enzyme expressed in humans. It acts to metabolize a wider number of clinically important drugs including warfarin. *CYP2C9* is highly polymorphic gene and more than 30 variant for this gene are known. The wild type allele, *CYP2C9*1* is associated with normal enzyme activity. A number of allelic variants of the *CYP2C9* gene are associated with decreased enzyme activity and lower clearance rate of warfarin. Of these two variants, *CYP2C9*2* (Arg144Cys) and *CYP2C9*3* (Ile359Leu) are very common. The frequency of different *CYP2C9* alleles varies between ethnic groups. *CYP2C9-*2* and **3* alleles are most frequently found in the Caucasian population than Asian or African populations. Whereas in African Americans totally different alleles, *5,*6, *8 and *11 confer this variability.[6,9,10,11]
Another very impotant enzyme playing imperative role in warfarin activity is Vitamin K 2,3 epoxide reductase enzyme complex (VKORC). The *VKORC1* gene encodes the C1 subunit of this enzyme complex and controls the steps which are concerned with recycling of vitamin K. The warfarin drug targets this complex. A very common non coding variant, -1639G>A in the promoter region of *VKORC1* gene lowers the protein expression by altering a transcription factor binding site. Low protein expression results into increased sensitivity to warfarin. Again frequency of -1639G>A allele varies between different ethnic groups. It has been suggested that this could be the reason for low warfarin dose required by the patients from Asian descent.[7] So it has been observed that polymorphism in *VKORC1* and *CYP2C9* genes significantly influence the warfarin dose requirement. A study on northern Indian population shows that *VKORC1* 1639 G>A polymorphism is present at quite high frequency in the people. Single nucleotide polymorphism (SNPs) in *VKORC1* gene has been connected with the reduced efficacy of vitamin K recycling due to the lesser activity of *VKOR*. The *VKORC1* -1639 G>A variant is genotyped in different populations. This polymorphism has varible frequency between different ethnic groups.[8]
It has been observed that Caucasians and African-Americans require significantly higher warfarin dose than Asians to achieve the desired INR. African, African American, Indian, Omanian, Romanian, United Kingdom and French people need higher dose of warfarin to achieve the desired INR, this is because in *VKORC1* -1639 G>A polymorphism they contain "G" allele as the wild allele its frequency in these populations is 97.8%, 87 %, 85.78%, 69.62 %,[11] 58.10 %, 52.6%, and 52%, respectively and all further these populations contain "A" as minor allele. On the other hand Japanese and Chinese people need very low dose of warfarin even one fourth of 5mg tablet of warfarin to achieve the desired anticoagulant target. The

reason behind is that these populations have "A" allele of *VKORC1* -1639 G>A as wild allele and "G" allele in these populations is the minor allele with frequency 9.9%, and 8.4 %, respectively.

There is strong evidence regarding of gene polymorphism and hence inter-individual variability in the dosage requirement of warfarin, to achieve the desired anticoagulation target, which is based on genetic factors as well as environmental factors. This provides the rationale for the future researches on gene polymorphism in Pakistani population so that appropriate dosage of the anticoagulant therapy be suggested in our multi ethnic population. This would certainly help in improving the prognosis of patients with health conditions, like venous thrombosis, pulmonary embolism, thromboembolic complications of atrial fibrillation and mechanical prosthetic heart valves.

References

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