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Dose Adjustment of Warfarin in Patients with Genetic Differences

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Abstract

*Warfarin is a powerful anticoagulant that, when administered wisely and well managed, results in significant reductions in morbidity and death from thromboembolic events. Even with careful monitoring, however, the commencement of warfarin administration is linked with extremely varied reactions across individuals and difficulties obtaining and maintaining levels within the restricted therapeutic range, which can lead to adverse pharmacological events. Variations in the genes encoding the enzymes cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase (CYP2C9) are the most closely connected to warfarin dosage needs (VKOR). Patients using warfarin who have one or more genetic polymorphisms in CYP2C9 and VKORC1 are more likely to experience adverse medication events and require large dosage reductions to obtain a therapeutic international normalised ratio (INR). The findings of this study imply that the CYP2C9*2 and CYP2C9*3 polymorphisms are associated with an increased risk of over anticoagulation and bleeding episodes in patients using warfarin anticoagulant, albeit the limited sample size in certain cases urges caution in interpretation. Screening for CYP2C9 variations assists doctors in developing new needed dose strategies and surveillance procedures in warfarin patients to limit the risk of adverse effects (14). The theme of this review sought to describe the role of CYP2C9*2 and CYP2C9*3 variations in anticoagulation and bleeding events in warfarin treatment.*

Keywords: *Thromboembolism, CYP2CP; Dosage Adjustment, Warfarin, VKORC1*

INTRODUCTION

The most widely given anticoagulant, warfarin, has a high interpatient variability in dosage needs. Warfarin therapy is difficult to manage due to patient response variability caused by a variety of variables such as medication, food, and disease-state interactions. Some of the variability in warfarin dose is explained by patient-specific characteristics (e.g., age, body size, race, concomitant conditions, and medicines), but genetic factors influencing warfarin response explain a considerably greater fraction of the variability in dose. Warfarin is largely metabolised in the liver by CYP2C9 and acts as an anticoagulant by blocking the protein vitamin K epoxide reductase complex, subunit 1. (VKORC1). Three single nucleotide polymorphisms (SNPs), two in the CYP2C9 gene and one in the VKORC1 gene, have been discovered to have important roles in regulating how warfarin medication affects coagulation. The CYP2C9 and VKORC1 genotypes of a patient can be utilised to assist identify the best beginning dosage of warfarin. The CYP2C9 gene encodes one of the primary enzymes involved in warfarin metabolism. Several mutant CYP2C9 alleles have been linked to decreased enzyme activity and poorer warfarin clearance rates. Patients with at least one copy of a variant allele (such as CYP2C9*2 and CYP2C9*3) have decreased metabolism, resulting in greater warfarin doses. They require less warfarin per day on average than people who are homozygous for the wild-type CYP2C9*1 genotype. The dose of warfarin must be customised for each patient based on their INR response and the disease being treated.

Gene association Studies:

Candidate-gene association studies(2-5) have identified 2 genes responsible for the main proportion of the genetic effect: CYP2C9, which codes for the enzyme cytochrome P450 2C9 that metabolizes S-warfarin(4)and VKORC1, which codes for warfarin's target, vitamin K epoxide reductase.(5,6)The influence of CYP2C9 and VKORC1 has also been confirmed by genome-wide association studies among whites.(7-8)Among whites and Asians, VKORC1 polymorphisms have shown a consistently significant influence on warfarin response, accounting for 11% to 32% of the variability in dose (9-10)Among North American blacks,

VKORC1 polymorphisms account for 4% to 10% of the variability in dose.

Warfarin and dosing variability:

Individual dose of warfarin varies greatly. Nongenetic variables (drug-drug interactions, environmental factors such as nutrition, alcohol intake, and smoking) and genetic factors all influence warfarin dose. There is considerable evidence that hereditary factors account for around 40% of warfarin dose variability.

Table: 1 FDA-Approved Warfarin Dosing

Allele	**CYP2C9**					
	*1/*2 (Extensive Metabolizer)	*1/*2 (Intermediate Metabolizer)	***1/*3** (Slow Metabolizer)	*2/*2	*2/*3	*3/*3
VKORC1 GG (Normal)	5.7mg	5.7mg	3.4mg	3.4mg	3.4mg	0.5-2mg
VKORC1 AG (low Sensitivity)	5.7mg	3.4mg	3.4mg	3.4mg	0.5-2mg	0.5-2mg
VKORC1 **AA** Halo type (High Sensitivity)	3.4mg	3.4mg	**0.5-2mg**	0.5-2mg	0.5-2mg	0.5-2mg

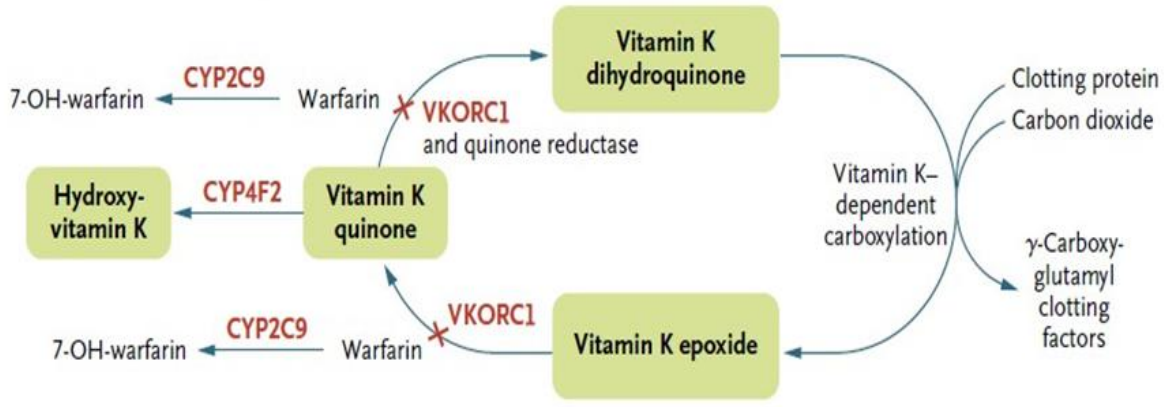

Figure: 1Mechanism of action of warfarin

- Warfarin works by inhibiting Vitamin K Epoxide Reductase (VKOR)
- VKOR helps recycle vitamin K which is important in proper functioning of clotting factors
- By inhibiting VKOR, warfarin alters the vitamin K cycle and results in the production of inactive clotting factors
- Polymorphisms exist in the gene for VKOR (VKORC1)

➢ VKORC1 (-1639 G/A) reduces vitamin K to make activated clotting factors
- G allele: normal expression of VKOR
- A allele: decreased expression of VKOR

➢ Lower dose requirements needed in -1639 G/A
➢ Lowest dose requirements needed in -1639 A/A

Table: 2 Percentage of VKORC1 genotypes.

VKORC1 (-1639 G/A)	AA	AG	GG
Caucasians	19%	56%	25%
Spanish	32%	40%	28%
Chinese	80%	18%	2%
African-Americans	0%	21%	79%

CONCLUSION

VKORC1 and CYP 2C9 polymorphisms have been examined in the context of warfarin treatment. Pharmacogenetics, a new and emerging discipline, may one day allow physicians to customise a patient's warfarin dosage. However, because pharmacogenetics is still in its early stages, further clinical trials, particularly prospective randomised studies, are required to acquire a complete knowledge of the actual implications in terms of efficacy and cost of such gene-guided drug therapy. Another study concern that should be addressed is if genotypes require a distinct target INR, as there may be a significant overlap in dosage requirements with individuals who do not have the genetic variations.

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