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THE EFFECTS OF GENETIC AND NON GENETIC FACTORS ON WARFARIN DOSE RESPONSE IN VENOUS THROMBOEMBOLISM

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ABSTRACT **BACKGROUND** Warfarin is the most commonly used oral anticoagulant for the treatment and prevention of thromboembolic disorders. Pharmacogenomics studies have shown that variants in CYP2C9 and VKORC1 genes are strongly and consistently associated with warfarin dose variability.

METHODOLOGY In this review, we included patients on stable warfarin dose and had the genetics and non-genetics factors associated with mean warfarin dose. We searched PubMed, Medline, Scopus, Google scholar and reference lists of relevant reviews.

CONCLUSION Genetic and non-genetic factors affects the dose of warfarin. Genetic factors and Non genetic factors plays a significant role and that may affects the dose of warfarin.

KEYWORDS : Genetic and Non genetic factors, CYP2C9 & VKORC1, Warfarin, Venous thromboembolism

INTRODUCTION

Pharmacogenetics and pharmacogenomics focus on interaction between genes and drugs. Variability in pharmacogenetically relevant genes is the most important cause of variation in drug response[1]. Interplay of various factors like environment, genetic and disease determinants evaluates the profile of plasma concentration for a drug[2,3]. The optimal dose of warfarin for patients of venous thromboembolism, the third most common cardiovascular disease including deep vein thrombosis and pulmonary embolism to bring about morbidity and mortality[4]. The anticoagulant effect of warfarin, an oral anticoagulant is due to inhibition of carboxylation of vit k dependent proteins[5]. Its therapeutic efficacy and toxicity varies from individual to individual, about 90% of human variations are based on single nucleotide polymorphism. The remaining differences are due to deletions, insertions, microsatellites and tandom repeates [6]. SNPs have been linked to the variations observed in efficacy and toxicity for warfarin .

Apart from genetic factors non genetic factor like age, sex body weight, height comorbidities habits (smoking, drinking) are the major contributors for variability in the dose of warfarin. Information on the effect of non genetic factors on the dose of warfarin are scattered. The present study is an honest approach of bringing down important information about the variability of warfarin dose based on genetic and non genetic factors.

MATERIALS AND METHOD

STUDY PLAN:

Last Five years (2014-2019) published medical and genetic literature was searched on the website www.ncbi.nlm.nih.gov using Boolean query technique with medical sentences and MeSH terminologies like CYP2C9 & VKORC1 polymorphism in venous thromboembolism. Further the search result was filtered using article type (review research), text availability (free full test abstract), publication date (5 years) and species (human) options. Article were downloaded and evaluated to extract useful information.

DISCUSSION:

NON GENETIC FACTORS:

Racial difference is a well-known predictor for variation in disease incidence prevalence its diagnosis, treatment strategy and outcome. Few observational studies have concluded that racial difference may be one of the crucial factor to decide the dose of warfarin to be used. Among European Americans and African Americans[7] effect of Clinical and genetic factors on warfarin dose differs by race[7]. Racial factor has been considered as an important predictor in designing the two dosing algorithm-warfarin dosing algorithm[8] and International Warfarin Pharmacogenetic Consortium (IWPC) [9]. Further many multicentric clinical trial are necessary to explore the effect of racial difference on the dosing of warfarin among other races worldwide.

Other non genetic factors like age, BMI, smoking, co-medications influences warfarin dose. When compared, the affect of genetic and non genetic factors, the non genetic factors played less important but existent role on the variability in warfarin dose necessities [10-12]. A study shows significant affect of non genetic factors like age Body Mass Index (BMI), smoking status, concurrent use of other antiplatelet medications and interacting medication like amiodarone on the warfarin dose requirement. Among all age accounted for the maximum portion followed by amiodarone, BMI, other antiplatelet medications and smoking status in sequence [13]. Another study done in china revealed no significant effect of sex, significant and negatively correlated effect of age and significant positively correlated effect of body weight, height, body surface area, on the dose of warfarin [14].

GENETIC FACTORS

CYP2C9

CYP2C9 is a metabolizing enzyme predominantly expressed in liver and responsible mainly for S-warfarin and many other drugs. Till date 60 number of CYP2C9 have been found. Among all 37 are functional and only 31 are of medical interest for affecting the maintenance dose of warfarin[15]. Pharmacokinetic is moderated by polymorphic cytochrome P450-2C9 (MIM 601130) through hydroxylation[16]. The two isoform i.e R-warfarin is metabolized by CYP2C9 while s-warfarin is metabolized by other CYP isoform. A study done among Ashkenazi and Sephardi Jewish populations to understand the sensitivity towards warfarin treatment concluded that different genotype of CYP2C9 and VKORC1 show different sensitivity and resistance[16]. The impact on genetic variation on the variability of drug dose of warfarin/acenocoumarins may be upto 30-90%[17] depending on type of polymorphism mutant alleles. Among 5 different mutant alleles (CYP2C9*1- CYP2C9*5) CYP2C9*1 is the most common variant. The two most widely studied alleles are CYP2C9*2 and CYP2C9*3[18]. The increased sensitivity towards warfarin is may be because of lesser metabolic capability of polymorphic alleles of CYP2C9. CYP2C9*2 and CYP2C9*3 decreases the warfarin metabolism by 30%-50% and 90% respectively[19-21]. After the thorough screening of CYP2C9 alleles the two alleles i.e. CYP2C9*2 and CYP2C9*3 were found to be commonly present in south Indian population with DVT. These were further classified into homozygous and heterozygous alleles. Presence of different types of alleles divide the patients to normal intermediate and poor metabolizers[17]. In contradiction, it has been found that the variants CYP2C9*2 and CYP2C9*3 are either rarely or not at all present in Asian population[14].

VKORC1

Pharmacodynamics of warfarin is moderated by VKORC1 genes (MIM 608547)[16]. A study done among Ashkenazi and Sephardi Jewish

populations to understand the sensitivity towards warfarin treatment concluded that different genotype of VKORC1 show different resistance toward warfarin treatment[16].

Warfarin produces its action by binding with vitamin K epoxide reductase and form vitamin K epoxide reductase complex subunit 1 so that there is less availability of activated Vitamin K for coagulant action[22,23]. SNPs of VKORC1 produces greater sensitivity towards warfarin dose hence the requirements of warfarin is lesser.

Five SNPs of VKORC1 can be frequently found among the population and depending on their effect on warfarin dose they are grouped in haplotype A or haplotype B group[24]. As many as nine haplotypes of VKORC1 has been identified (Reider et al) which may affect the dose of warfarin[18]. 99% genetic variability of VKORC1 is among (VKORC1*2:41%,VKORC1*3: 38%, and VKORC1*4:20%) [25]

CONCLUSION:

All together both genetic and non-genetic factors affects the dose of warfarin. Genetic factors play a significant role in this. Non-genetic factors like age, body weight, habits, plays no less role and may significantly affects (especially in people with comorbidities) the dose of warfarin.

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