Study of VKORC1 polymorphism (C1173) In Egyptian population

Thesis

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Summary and Conclusion

Warfarin is the most commonly used oral anticoagulant with a narrow therapeutic range of efficacy and can lead to hemorrhagic or thromboembolic events even under careful dose titration, it has large inter-individual dose variability and inter-ethnic differences in the dose required for its anticoagulation effect. The most important genes that contribute to its therapeutic effect, are Vitamin K epoxide reductase complex subunit 1 (VKORC1) and cytochrome P 450 2C9. VKORC1 1173 C>T is a common polymorphism in VKORC1 that affect the interindividual variability of warfarin dose and the most important polymorphisms in CYP2C9 are CYP2C9*2 and CYP2C9*3.

The aim of the present study is to determine allele frequency and genotype distribution of VKORC1 1173 C> T, CYP2C9*2 and CYP2C9*3 variant polymorphisms in Egyptian population and to further evaluate the influence of these variants polymorphisms on the inter-individual differences in warfarin dosage.

SYBR Green-based multiplex allele-specific real time PCR was used for detection of VKORC1 (C1173T), CYP2C9 *2 (C430T) and *3 (A1075C) polymorphisms in 200 Egyptian individuals, 46 of them, were receiving warfarin and the other 154 were age and sex matched control volunteers.

Frequency of VKORC1 1173 C>T alleles were 23% for allele C and ٧٧% for allele T which was the more frequent allele. Genotype prevalence for VKORC1 variants were as follow: 11%, 24% and ٦٥% for CC, CT and TT genotypes respectively, where TT genotype was the most frequent genotype.

Frequency of CYP2C9 alleles were as follow: 87.6%, 6.49% and 5.84% for CYP2C9 *1, *2 and *3 respectively, the most frequent allele was CYP2C9 *1 (wild allele).

Frequency for CYP2C9 haplotypes in Egyptian populations were as follows: 81% for *1/*1, 3.٢% for *1/*2, 9.74% for *1/*3, 4.56% for *2/*2 and 0.65% for each of *2/*3 and *3/*3, the most frequent haplotype was CYP2C9 *1/1* (wild haplotype).

VKORC1 TT genotype was associated with a significantly lower warfarin dose compared to both the wild CC genotype and the heterozygous CT genotype,

while CYP2C9*2/*2 haplotype was associated with a significantly lower warfarin dose in comparison to the 1*/1* wild haplotype.

Bleeding related to warfarin intake occurred in 17 out of the 46 patients (37%), comparing between different VKORC1, CYP2C9*2 and CYP2C9*3 polymorphisms and wild type genotypes as regards the incidence of bleeding; CYP2C9*2 CT, TT and CYP2C9*3 AC had a significantly higher incidence of bleeding compared to their wild genotypes.

Thrombotic complications under warfarin treatment occurred in 11 out of the 46 patients (24%), however different VKORC1, CYP2C9*2 and CYP2C9*3 polymorphisms did not show any statistically significant difference in the incidence of thrombosis when compared to the wild genotypes.

VKORC1 1173C>T, CYP2C9*2 and CYP2C9*3 variant polymorphisms are associated with the inter-individual differences in warfarin dosage and the risk of side effects in Egyptians. VKORC1 is likely to contribute more in inter-individual differences in warfarin dosage than CYP2C9.

Our results showed that age, sex, weight and genetic polymorphisms accounted to 61.3% of the inter-individual variations in warfarin dose.

We could formulate a simple equation for personalized warfarin dosing based on different CYP2C9 haplotypes and VKORC1 (1173) genotypes.

In conclusion, our results may help in better understanding the molecular genetic basis underlying Egyptians' differences in response to warfarin. VKORC1 and CYP2C9 allele 2* and 3* genetic testing is technically feasible, and likely to improve the clinical management of anticoagulation by tailoring drugs to patients in order to achieve maximum efficacy and minimum toxicity preventing adverse Reactions.