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(CASE REPORT)

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Case report on Pharmacogenetic guided warfarin dosing in a postoperative valve replacement patient

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Abstract

Patient underwent mitral valve replacement with mechanical valve and was initiated on oral anticoagulation with standard dose of warfarin. She developed supra therapeutic INR levels. Genotyping of CYP2C9 and VKORC1 encoding genes revealed homozygous variation of CYP2C9*3*3 and heterozygous variation of VKORC1 G>A making her hypersensitive to warfarin. Based on this study result and Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline, a low dose of warfarin (0.5mg per day) was prescribed, to achieve a therapeutic INR of 2.5 to 3.5 and adverse drug effects were avoided.

Keywords: Warfarin; Pharmacogenetics; CYP2C9; VKORC1

1. Introduction

Patients who have undergone mechanical valve replacements need lifelong anti-coagulation. Warfarin is the commonly used oral anticoagulant and it prevents Vitamin K recycling by inhibiting the Vitamin K epoxide reductase enzyme (VKOR), which is encoded by VKORC1 G/G gene. Warfarin is inactivated by the hepatic CYP2C9 enzyme, which is encoded by CYP2C9*1 gene (1).

Warfarin has a narrow therapeutic index and a wide inter-patient variability in the dose required to maintain a target INR value (2). Mutation in the genes that encode the above enzymes, results in poor warfarin metabolism, delayed clearance, weak target enzyme, increased warfarin sensitivity, supra therapeutic INR and adverse effects in the form of hemorrhagic complications (3).

Pharmacogenetic analysis helps us to identify patients who have these mutations and enable us to tailor warfarin dosage accordingly.

2. Case report

2.1. Clinical course

A 35 years old female patient presented to us with rheumatic heart disease, severe calcific mitral stenosis and with NYHA class III symptoms. She had completed her family with two kids. She underwent Mitral valve replacement with 25 mm ATS mechanical heart valve. The procedure was uneventful and she came off bypass with regular rhythm and minimal inotropic support.

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On postoperative day 1, she was started on Tab Warfarin 3 mg supplemented with low molecular weight heparin. On post operative day 3, she had supra-therapeutic INR of 9. She did not have any bleeding manifestations. In view of her increased INR levels, warfarin was temporarily withheld, Injection Vitamin K 10 mg and 2 units of fresh frozen plasma were given. In view of her supra therapeutic response to Warfarin, it was decided to do genetic analysis to check for mutation in the genes coding for enzymes involved in Warfarin metabolism.

2.2. Genetic analyses

From the patient's blood sample, DNA was isolated. PCR amplification of the DNA sequence was done using biotinylated primers. Hybridization of the amplification products to a test strip containing allele specific oligonucleotide probes immobilized as an array of parallel lines. Bound biotinylated sequences are detected using streptavidin-alkaline phosphatase and color substrates. The assay covers 3 polymorphic loci: VKORC1- 1639 G>A, CYP2C9430 C>T(2C9*2), CYP2C9 1075 A>C (2C9*3). Test was performed using PGX-ThromboStripAssay (ViennaLab Diagnostics GmbH).

3. Results

It was found that she had homozygous mutant form of CYP2C9 3*3*, making her poor warfarin metabolizer. She was also found to have heterozygous mutant form of VKORC1 -1639 G>A, which makes her to have increased sensitivity to Warfarin. This in turn relates to her highly sensitive response to standard dose of warfarin. INR was rechecked and warfarin was cautiously re-started. The patient achieved a therapeutic level of INR of 3.5 even at a low dose of warfarin of 0.5 mg per day.

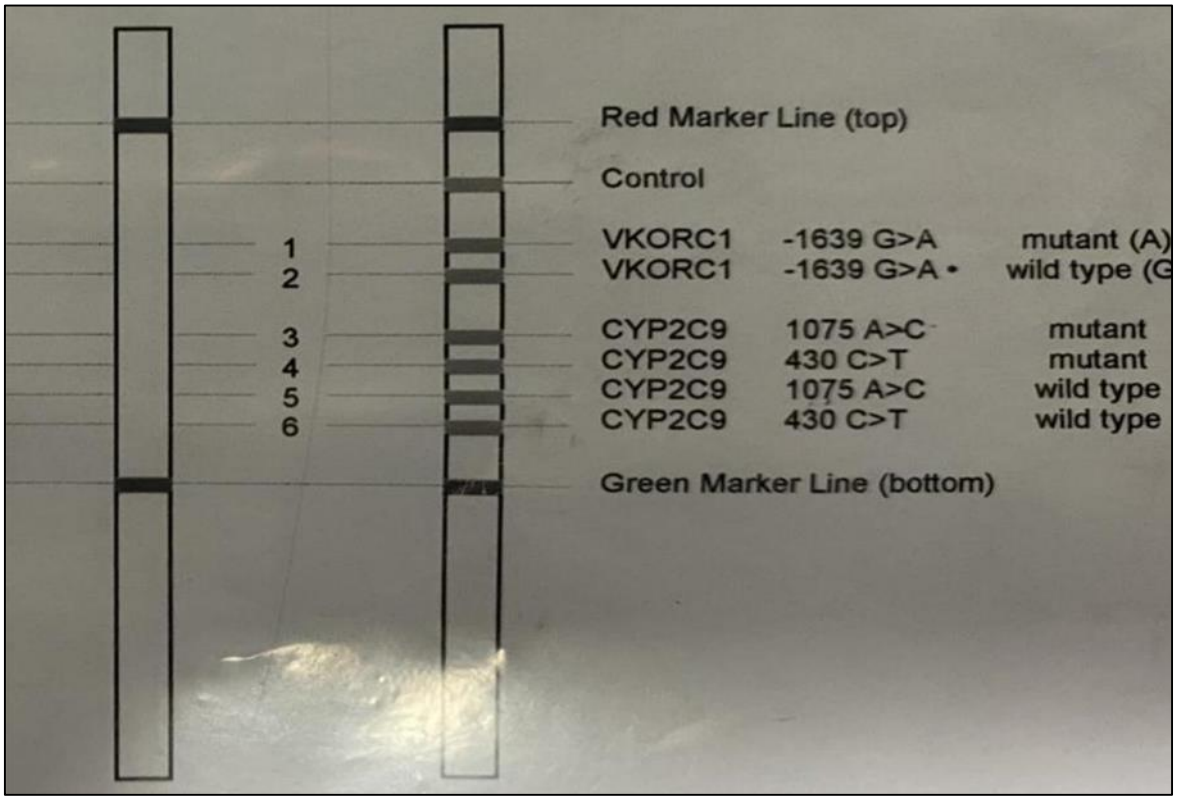

Figure 1 ThromboStripAssay showing homozygous variant of CYP2C9 3*3* and heterozygous variant of VKORC1 -1639 G>A

4. Discussion

Single nucleotide polymorphisms in the CYP2C9 gene and the VKORC1 gene is present in nearly 40% of Indian patients (4).

CYP2C9 has 3 variants. CYP2C9*1 variant will metabolize warfarin normally whereas CYP2C9*2 variant and CYP2C9*3 variant reduce warfarin metabolism by 30-40% and 80-90% respectively (5).

VKORC1 variant wherein G allele is replaced by A allele, less VKORC1 enzymes are produced (6).

In the presence of these two mutations, there will be hypersensitivity to warfarin because of its delayed clearance from the body and decreased levels of target enzyme, resulting in supra therapeutic levels of INR and increased risk of bleeding manifestations (7).

Our patient was a homozygous mutant for CYP2C9*3*3 and heterozygous mutant form of VKORC1 -1639 G>A making her extremely sensitive for warfarin. She therefore needed a low dose of 0.5 mg of Warfarin to achieve a therapeutic INR of 3.5.

The suspicion of probability of genetic mutation in warfarin metabolism and performing the analysis timely, helped in correct titration of the dose of Warfarin and prevented any further complications.

5. Conclusion

Single nucleotide polymorphisms of genes encoding enzymes responsible for warfarin metabolism are associated with higher incidence of adverse drug effects. Genotype guided warfarin dosing to achieve the optimum target level of INR is safe and efficacious.

Compliance with ethical standards

Acknowledgement

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Disclosure of conflict of interest

There is no conflict of interests regarding the publication of this paper.

Statement of informed consent

Informed consent obtained from the patient.

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