Review Article **ISSN: 2349 – 4492**

Asian Journal of Research in Biological and Pharmaceutical Sciences

Journal home page: www.ajrbps.com

https://doi.org/10.36673/AJRBPS.2021.v09.i04.A17

A STUDY ON IMPACT OF CYP2C9 ENZYME INVOLVING IN INTERACTING DRUGS ON WARFARIN AND ITS PHARMACOGENOMICS

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ABSTRACT

A Study on participants predicted to be sensitive responds to warfarin drug based on CYP2C9 and VKORC1 genotypes, had significantly greater international normalized ratio (INR) variability over time. The associations of INR variability with genotype was done by the subgroup family is not exposed to interacting drugs, whereas the effect of interacting drug exposure was driven by the subgroup categorized as normal responders. It's that findings emphasize the importance of considering drug interactions in pharmacogenomic studies.

KEYWORDS

Pharmacogenomics, VKORC1 genotype and CYP2C9.

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INTRODUCTON

It can be difficult to predict who will be benefit from medications, who will not respond at all, and who will experience negative side effects (called adverse drug reactions). These are genetic differences between will be used to predict whether a medication will be effective for a particular persons and its to help prevent adverse drug reactions. Conditions that have affect a person's response to certain drugs include clopidogrel resistance, warfarin sensitivity, warfarin resistance, malignant hyperthermia, Stevens-Johnson syndrome/toxic epidermal necrolysis, and thiopurine S-methyltransferase deficiency.

This enzyme is metabolized by oxidation and of both xenobiotics, including drugs, and endogenous compounds, including fatty acids.

METHODS

Study cohort

Those are 11,426 participants, 402 met all inclusion criteria for our study. Despite the introduction of direct oral anticoagulants in 2010, warfarin remains the most widely prescribed anticoagulant 1, 2 as well as one of the drugs responsible for the largest numbers. The combination of a narrow therapeutic index and the potential to precipitate life-threatening adverse events made warfarin an attractive candidate for precision dosing algorithms are based on pharmacogenomics. Which could 2Clinical and Translational Science Drug Interactions and Warfarin Pharmacogenomics agrawal *et al*. Dilute an underlying effect associated with cytochrome P450 (CYP) 2C9 and vitamin K epoxide reductase complex (VKORC)1 genotype present in more typical clinical settings. However, the three most commonly cited pharmacogenomics-based warfarin dos-ing algorithms 6-8 variably consider CYP2C9-interacting drugs with amiodarone being the only drug in common. In this study, we investigated the association of long-term measures of warfarin anticoagulation efficacy and stability with CYP2C9/VKORC1 genotype and concurrent use of CYP2C9-interacting drugs in a retrospective clinical setting.

YP2C9 inhibitors and inducers

The FDA label for warfarin, and the Flockhart Table of Drug Interactions. 15 This yielded 34 candidate CYP2C9-interacting drugs. We omitted 14 because they were not prescribed in this cohort. A literature search was done for the remaining 20 drugs looking for evidence that the drug was a CYP2C9 inhibitor or inducer, and evidence of a clinically significant interaction with warfarin. This analysis, summarized in the Supporting Information, identified 10 CYP2C9 inhibitors and 3 CYP2C9 inducers as the interacting drugs considered in this study.

We examined exposure to CYP2C9-interacting drugs by counting the number of unique medications taken during warfarin therapy. Participants were then stratified into three categories based on this number: 0 interacting drugs, 1 interacting drug, or 2 or more (2+) interacting drugs.

We did not differentiate between CYP2C9 inhibitors and inducers when assigning these categories. Notably, exposures to multiple interacting drugs did not have to coincide as long as each exposure independently overlapped with the warfarin course of a given participant.

Impact of concurrent CYP2C9-interacting drugs on INR

The impact of exposure to CYP2C9-interacting drugs on anticoagulation was evaluated by examining INR values immediately surrounding the start date of each concurrently prescribed medication. Importantly, each separate exposure was included in this analysis, even when there were two unique courses of the same drug. INR values obtained on the same day were not averaged for this analysis to lower the risk of masking short-lived peaks and troughs. The study period from which INR values were sampled was defined by a minimum date (30 days before the start of the medication), and a maximum date defined as the earlier date between 30 days after the start date and 7 days after the end date. More detailed definitions of the study period are found in the Supporting Information.

DATA ANALYSIS

All statistical analyses were conducted using SPSS Statistics and specific tests are described in the Results. All tables and figures, except Figure S2, were generated using SPSS Statistics. One-way analysis of variance (ANOVA) and $\chi 2$ tests was utilized to compared descriptive variables, such as age and sex, across combined genotype categories (normal responder, sensitive responder, and highly sensitive responder), and medication exposure categories (0, 1, 2+). One-way ANOVA were done with subgroups defined as by combined genotype and medication exposure. Comparisons of absolute INR changes before and after starting a given CYP2C9-interacting medication was performed using t-tests.

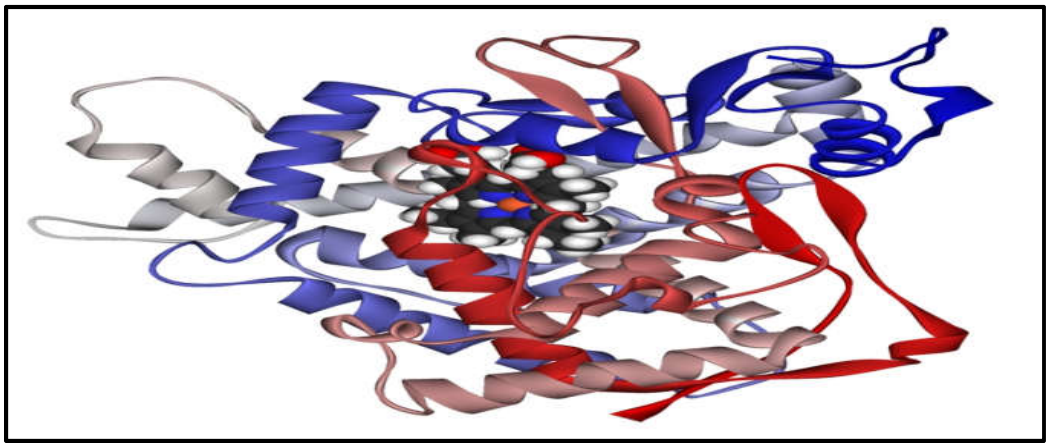

Figure No.1: CYP2C9 gene

CONCLUSION

A Study on participants predicted to be sensitive responds to warfarin drug based on CYP2C9 and VKORC1 genotypes, had significantly greater international normalized ratio (INR) variability over time. The associations of INR variability with genotype was done by the subgroup family is not exposed to interacting drugs, whereas the effect of interacting drug exposure was driven by the subgroup categorized as normal responders. It's that findings emphasize the importance of considering drug interactions in Pharmacogenomic studies.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Priyadarshini Institute of Pharmaceutical Education and Research, 5th mile, Puladigunta, Guntur, Andhra Pradesh, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Monica Sharon Patchala *et al*. A study on impact of cyp2c9 enzyme involving in interacting drugs on warfarin and its pharmacogenomics, *Asian Journal of Research in Biological and Pharmaceutical Sciences,* 9(4), 2021, 124-127.