Determination of the relationship between CYP2C9 genotype and daily warfarin dose requirement in children on anticoagulation therapy.

Victor Ibubeleye* (BSc. Pharmacology) , Anne Lakey and Farhad Kamali
Institute of Cellular Medicine, Newcastle University, UK
(109292531. v.t.t.ibubeleye@ncl.ac.uk)

INTRODUCTION

Warfarin is a widely prescribed drug for anticoagulation and exerts its effect by inhibiting vitamin K recycling in the coagulation cascade. It has a narrow therapeutic index and as such, much care is needed in deciding a suitable dose for patients. Warfarin is mainly metabolised by the CYP2C9 enzyme in the liver and the drug metabolite is subsequently excreted from the body. CYP2C9 exhibits genetic polymorphism; mutations in the CYP2C9 gene lead to the expression of variant forms of the enzyme with reduced catalytic activity.

This study aimed to establish the relationship between CYP2C9 genotype and daily warfarin dose requirement in paediatric patients on anticoagulation therapy.

METHOD

- 120 children on chronic therapy with warfarin took part in this study
- A venous blood sample (5ml) was taken for later genotyping (for CYP2C9) and plasma warfarin concentration determination (by HPLC).
- Data obtained were subjected to statistical tests for association between genotypes and plasma concentrations

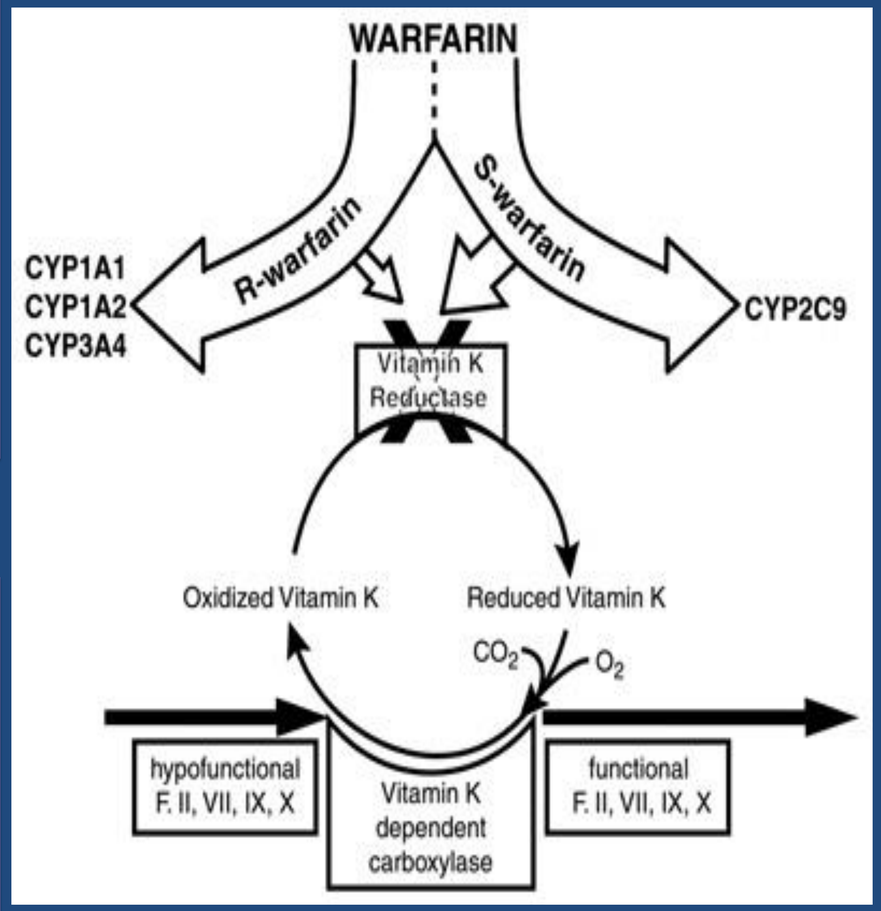

Figure 1. Metabolic pathway of warfarin enantiomers. (Source: American Association for Clinical Chemistry)

RESULTS

- Log (S-warfarin clearance) and (R-warfarin clearance) gave a normal distribution.
- The number of CYP2C9 *2 and CYP2C9*3 are both significant for loge(S clearance) explaining 16.6% of the variability, with the number of *3 having twice as large effect as the number of *2.

CONCLUSION

- The study successfully showed an association between CYP2C9 genotype and S-warfarin clearance.
- This therefore emphasises the need for clinicians to prescribe warfarin in accordance with the CYP2C9 genotype the patient possesses.

REFERENCES

1. Aithal GP, Day CP, Kesteven PJL, Daly AK. *Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications*.Lancet 1999;353:717-9

2. Biss, T.T et al (2012). *VKORC1 and CYP2C9 genotype and patient characteristics explain a large proportion of the variability in warfarin dose requirement among children*. Blood 119: 868-873

3. Haining RL, Hunter AP, Veronese ME, Trager WF, Rettie AE. *Allelic variants of human cytochrome P-450 2C9: baculovirus-mediated expression purification, structural characterization, substance stereoselectivity and prochiral selectivity of the wild-type and 1359L mutant forms*. Arch Biochem Biophys 1996;333:447-58.

ACKNOWLEDGEMENT

This project was sponsored by the Wellcome Trust Foundation for which the author is grateful.