UNIVERSITI TEKNOLOGI MARA

GENOTYPING OF CYP2C9 FOR CARDIOVASCULAR PATIENTS

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ABSTRACT

CYP2C9 lines the important drug-metabolizing cytochrome P450 isoforms in the human liver but linked with inter-individual variation in drug-response relationship due to single nucleotide polymorphism of the encoding gene. Modification of *CYP2C9* activity due to genetic factor alters the metabolism of drug substrates resulting in reduced efficacy or worse, toxicity. Amongst substrates of *CYP2C9*, warfarin is of special interest due to its narrow therapeutic index. The objective of this study is to determine the type and frequency of *CYP2C9* polymorphism among patients on warfarin therapy. We successfully genotyped 180 patients who were on warfarin from 183 samples. The genomic DNA was obtained from the gene pool of Universiti Teknologi Mara Pharmacogenomic Research Group.The DNA was genotyped for known *CYP2C9* polymorphic allelic (*CYP2C9*2, *3* and **4*) variants with the use of allele specific multiplex polymerase chain reaction and the product was resolved via gel electrophoresis. Polymorphic variants of *CYP2C9* (*CYP2C9*2* and *CYP2C9*4*) were not detected in these patients. Among the 180 patients, the genotype frequency of *CYP2C9*1/*1* was 92.7% and *CYP2C9*1/*3* was 7.3%. There was only two genotype expressed in patients on warfarin therapy, *CYP2C9*1/*1* and *CYP2C9*1/*3*. This provide a useful database to help physician predict the possibility of adverse drug reaction among patients on warfarin in Malaysia.

CHAPTER 1

INTRODUCTION

Cytochrome P450 is a key enzyme that catalyzes the metabolism of many clinically used drugs and also non-drug xenobiotics (Miners and Birkett, 1998). Changes in the amino acids composition is linked with inter-individual variation in drug-response relationship. A single nucleotide polymorphism alters its activity resulting in reduced efficacy or even worse, toxicity.

In the human liver, isoforms *CYP2C9* ranks among the other known member of CYP2C subfamily, which exhibit genetic polymorphism. Several drugs that are metabolized by *CYP2C9* includes losartan (Sica *et al.*, 2005), glibenclamida and glimepiride (Niemi *et al.*, 2002), torsemide (Miners *et al.*, 2000), warfarin (Schwarz, 2003), phenytoin (Goldstein, 2001) and several anti-inflammatory drugs such as ibuprofen, diclofenac and mefenamic acid (Goldstein, 2001). Many studies have reported mutation in the coding region of *CYP2C9*, however three allelic variants, *CYP2C9*2, CYP2C9*3* and *CYP2C9*4*, have been identified to influence drug metabolism. Among *CYP2C9* substrates, warfarin and phenytoin are of special interest due to their narrow therapeutic index.

Warfarin is an anticoagulant agent that is widely used in cardiovascular diseases despite its narrow therapeutic index. It is recommended that warfarin therapy is adjusted based on International Normalised Ratio (INR) ranging from 2-4 for the treatment and prophylaxis of thromboembolic diseases. However it is difficult to