

# CHAPTER 1

## INTRODUCTION

Drug responses in different individuals may be varied from either different concentrations of the drug at the site of action or from different physiological responses to the same drug concentration. Variation of drug response is one of the causes of therapeutic failure or drug-induced toxicity. Most drugs are metabolized by cytochrome P450 (CYP) enzymes which are under genetically controlled. Therefore one of the major causes of individual and interethnic variations in drug response is genetic polymorphism of the drug metabolizing enzymes.

Genetic polymorphism is a difference in deoxyribonucleic acid (DNA) sequence which was found at 1% or higher in a population (Vogel, 1959). These differences in DNA sequences encoded for drug metabolizing enzyme can lead to differences in drug metabolism.

Genetic polymorphism of cytochrome P450 2C19 (CYP2C19) was initially known as S-mephenytoin hydroxylation polymorphism because of the impairment of 4-hydroxylation of the S-enantiomer of mephenytoin. Mephenytoin (3-methyl- 5-phenyl- 5-ethylhydantoin, Mesantoin®) was used for the treatment of seizures in humans (Wilkinson *et al.*, 1989). Genetic polymorphism of mephenytoin metabolism was found in 1984 when one of the subjects felt very drowsy during the study of the pharmacokinetic of this drug and his urine concentration of the mephenytoin metabolite, 4-hydroxymephenytoin, was very low (Küpfer and Preisig, 1984).

Mephenytoin is available as a racemic mixture of R- and S-enantiomer. The S-enantiomer is rapidly hydroxylated to 4-hydroxymephenytoin (Wilkinson *et al.*, 1989) while the R-enantiomer is slowly metabolized by oxidative demethylation to phenylethylhydantoin (PEH or nirvinol). Genetic polymorphism of CYP2C19 is inherited by an autosomal recessive trait. Individuals can be characterized as either extensive metabolizers (EMs) or poor metabolizers (PMs) according to their ability to oxidize

CYP2C19 substrates. The aromatic S-hydroxylation of mephenytoin is a stereoselective step in the metabolism and is impaired in PMs (Wedlund *et al.*, 1985). The measurement of the S/R ratio of mephenytoin can be used to characterize the phenotype of CYP2C19 (Wedlund *et al.*, 1984; Sanz *et al.*, 1989).

CYP2C19 is also involved in the metabolism of the antipeptic ulcer drug, omeprazole (Andersson *et al.*, 1992). The plasma omeprazole/5-hydroxyomeprazole ratio correlates well with CYP2C19 genotype. It has been shown recently that a higher concentration of omeprazole in poor metabolizer resulted in greater gastric acid suppression as compared to extensive metabolizer (Chang *et al.*, 1995 and Furata *et al.*, 1999). Cure rates for *Helicobacter pylori* infection in patients receiving omeprazole and amoxicillin were found to be lower in extensive metabolizers as compared to poor metabolizers (Furata *et al.*, 1998). An understanding of the CYP2C19 phenotype in patients may therefore be useful for optimal therapy with omeprazole and possibly other drugs.

Genetic polymorphism of S-mephenytoin hydroxylation is one of the most widely studied polymorphism of the CYP enzymes in human because CYP2C19 is one of the important drug metabolizing enzyme in human and involve in the metabolism of a number of drugs, such as some barbiturates (Küpfer and Brance, 1985; Adedoyin *et al.*, 1994), diazepam (Bertilsson *et al.*, 1989), mephenytoin (Wilkinson *et al.*, 1989), a proton pump inhibitor that binds to the H<sup>+</sup>/K<sup>+</sup> ATPase e.g. omeprazole (Andersson *et al.*, 1990) and lansoprazole (Sohn *et al.*, 1997), certain tricyclic antidepressants (Baumann *et al.*, 1986; Skjelbo *et al.*, 1991; Sindrup *et al.*, 1993; Nielsen *et al.*, 1994), and antimalarial drug, proguanil (Ward *et al.*, 1991). This enzyme is also partially responsible for metabolism of certain  $\beta$ -blocker such as propranolol (Ward *et al.*, 1989), as well as metabolizes the HIV protease inhibitor nelfinavir to its major metabolite, which has an antiviral activity similar to that of nelfinavir itself (Lillibridge *et al.*, 1998). As a result, pronounced genetically determined differences in the disposition of these drugs may affect their efficacy and toxicity. In addition CYP2C19 polymorphism may contribute to a metabolic predisposition to certain diseases including non-aggressive bladder cancer

(Kaisary *et al.*, 1987), lung cancer squamous cell carcinoma (Benhamou *et al.*, 1997), scleroderma or systemic sclerosis (May *et al.*, 1990) and the eosinophilia-myalgia syndrome (Flockhart *et al.*, 1994). Thus defining the frequency of this polymorphism in different populations has considerable epidemiologic important.

The frequency of this polymorphism varies markedly in different racial populations, with the PM phenotype representing 2-5% in Caucasians (de Morais *et al.*, 1994a, 1994b; Balain *et al.*, 1995; Xiao *et al.*, 1997; Ibeanu *et al.*, 1998), 4-8% in Africans (Goldstein *et al.*, 1997), 13-23 % in Asians populations (de Morais *et al.*, 1994a, 1994b, Xiao *et al.*, 1997), and as high as 70% in the residents of Vanuatu in Malanesias (Kaneko *et al.*, 1997).

Most of the CYP2C19 studied in the Asians populations were performed in the East Asian populations (i.e. Chinese, Japanese or Korean). The information on the CYP2C19 polymorphism in the South-East Asian populations is still limited. The phenotype and genotype of North-Eastern Thai population has been studied and found that the two major defective alleles, *CYP2C19\*2* and *CYP2C19\*3*, cover almost all of the PMs in the North-Eastern Thai population (Tassaneeyakul *et al.*, 2002). Heterogeneity among the Thai ethnic particularly those who reside in the different part of the country is well recognized. The Southern Thais differ from the North-Eastern Thais in several aspects including living style, diet, culture and their ancestors. Therefore, present study was aimed to charecterize the genetic polymorphism of CYP2C19 in the Southern Thai population.