CHAPTER 5

DISCUSSION

The genetic polymorphism of CYP2C19 show interethnic difference in the distribution of PM traits. It is the primary cause of the wide interethnic differences in the metabolism of CYP2C19 substrates documented in several studies. Most of these studies were done in East Asian population. The data relating to genetic polymorphism of CYP2C19 in a Thais population is very limited. Two previous studies found that the prevalence of PMs in Thais population were significantly different. In 1994, Edstein *et al.* reported that the incidence of PMs for proguanil oxidation in their study was 18% but Tassaneeyakul *et al.*, 2002 demonstrated that the prevalence of PMs in the North-Eastern Thai population was only 6.5%. Due to the heterogeneity among the Thai ethnic, Southern Thais have different dialec and cultures from those who reside in the other part of the country. Our study aimed at the genotyping of CYP2C19 in Southern Thai population.

The EM phenotype consists of homozygous and heterozygous genotypes for the wild-type alleles while the PM phenotype consists of homozygous and heterozygous genotypes for the *CYP2C19*2* and *CYP2C19*3*. The prevalence of PMs in our study was 7.41% was not significantly different from the North-eastern Thai population. The present genotyping test confirmed that the prevalence of PMs in Thais was significantly lower than those reported in other South-East Asian (i.e Filipinos and Indonesians) populations and East Asian (i.e Chinese Japanese and Korean) populations (Table 11).

The results revealed that the allele frequencies of *CYP2C19*1, CYP2C19*2* and *CYP2C19*3* were 0.72, 0.27 and 0.02 respectively which were very similar to the previous study in the North-eastern Thai population. The present genotyping test confirmed that the frequency of *CYP2C19*2* is about 13 times greater than *CYP2C19*3*. The allele frequencies of *CYP2C19*2* determined in our study (0.27; 95% CI 0.21-0.33) was significantly lower than that found in Chinese-Han and Filipinos populations, but not

significantly different from that reported in Japanese and Korean populations (Table 12). Although *CYP2C19*3* is rare in Caucasians, this mutant allele appears to account for the remaining defective alelles in Asians PMs. The frequency of the *CYP2C19*3* allele in Southern Thai is similar to the North-Eastern Thai population but was significantly lower than the frequencies previously reported in other Asians populations (range 0.05 - 0.13).

The PMs have inactive CYP2C19 enzymes and therefore show poor ability to metabolize substrates of CYP2C19. Although the incidence of PMs of CYP2C19 of Thai population (that found in our study and previous study) are lower than those in other Asains population (about 7%) but there are important clinical implications because they are more prone to adverse drug reactions. Particularly, drugs in which CYP2C19 serves as the primary metabolic route of elimination or drugs with narrow therapeutic range e.g. mephenytoin and tricyclic antidepressants (TCAs). Severe adverse effects of TCAs appear especially after concomitant administration of a TCA with fluvoxamine or fluoxetine, inhibitors of both CYP2C19 and CYP2D6 (Caccia *et.al,* 1998). PMs of CYP2C19 require lower dose of phenytoin (Badyal and Dadhich, 2001). Therefore, PMs of CYP2C19 should avoided or used carfully with drugs that nawrow therapeutic index e.g mephenytoin, phenytoin and TCAs.

Proton pump inhibitors (PPI) such as omeprazole and lansoprazole are probe drugs that are widely used to study genetically CYP2C19 enzyme. The acid-inhibitory effects of normal doses of omeprazole and lansoprazole appear to be insufficient for patients with the homozygous EM of CYP2C19 in comparison with those with heterozygous EM or PM genotype status (Furuta *et al.,* 1999; Shirai *et al., 2002*; Sagar *et al., 2000*; dashi *et al., 2000*; Kita *et al., 2001*). Genotyping for CYP2C19 seems to be a useful tool for optimal treatment selection of PPI-based therapy for *H. pylori* eradication or gastroesophageal reflux disease. This may enable physicians to determine the duration of treatment and dosage regimen of PPI and determine the appropriateness of dual or triple therapy. Previous studies found higher cure rates of lansoprazole for *H. pylori* in the homozygous PMs of CYP2C19 (84.6%) and in heterozygous EMs (67.9%) compared with the homozygous EMs (45.8%) (Furata *et al.,* 2002). It was also found that the plasma

concentration of omeprazole and other PPI in the homozygous EMs genotype were the lowest among the 3 groups, i.e. homozygous PM, heterozygous EMs and homozygous EM (Furata *et al.*, 2001). This may be one of the possible explanations for the observation that therapeutic failure occurred more often in the homozygous EMs. Genotyping of CYP2C19 may save both money and time, at least in populations with a relatively high incidence of PMs of CYP2C19. Because of the current conventional triple therapy of *H. pylori* infection has some drawbacks (e.g. bacterial resistance to clarithromycin and metronidazole, adverse drug reactions and drug cost), there are suggestions that a high dosage of a PPI in a dual treatment regimen can achieve similar efficacy to the triple therapy regimen. Thus, it is possible that even homozygous EMs may benefit from genotyping information in the future. CYP2C19 genotyping may allow determination of an effective dosage regimen, including whether dual or triple therapy should be used. In the near future, it seems very possible that patients will be screened routinely for CYP2C19 genotype before PPI are prescribed.

The variety and usefulness of drugs metabolized by CYP2C19 suggest that there will be important clinical implications for genotyping of CYP2C19. Particularly drugs, in which CYP2C19 serves as the primary metabolic route of elimination or drugs with narrow therapeutic range, may represent those for which the genetic polymorphism is most likely to have clinical importance. Reliable phenotyping and genotyping tools are available for screening CYP2C19 activity in patients. Prediction of phenotype from genotype is a relatively simple task for CYP2C19, as the genotyping of an individual for CYP2C19 defective alleles, *CYP2C19*2* and *CYP2C19*3* can be use to identified EM or PM with high accuracy (>99%). Since the incidence of PM patients who carry CYP2C19 allele other than *CYP2C19*2* and *CYP2C19*3* would appear to be less than 1%. Therefor, CYP2C19 genotyping is sensitive as well as specific. Simple genotyping tests are avialable for the two most frequent alleles and so it is now possible to screen relatively large groups of patients or volunteers relatively quick.

In summary, the elimination rate of drugs from the body is a major determinant of both the intensity and duration of drug action and side effects. Variability of drug

metabolism is responsible for the pronounced interindividual differences in plasma concentration when patients receive the same dose of a drug. Among the drug metabolizing enzymes, CYP enzymes play a pivotal role in the elimination process. For genetic polymorphisms of CYP2C19, PMs may have higher plasma drug concentrations and may suffer from higher side effect compare to EMs. Thus selection of dose based on the patient's genotype could improve the efficacy and safety of drug therapy.