J. Toxicol. Pub. Health
Vol. 17, Supplement, pp. 145-155, 2001

Interethnic Variations of CYP2C19 Genetic Polymorphism

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ABSTRACT *: Cytochrome P4502C19 (CYP2C19) is one of human polymorphic xenobiotic-metabolizing enzymes. The enzyme has been reported to catalyze more than 70 substrates, involving more than 100 reactions. These include several classes of therapeutic agents (e.g. anti-microbial, cardiovascular, psychoactive, etc.), sex hormones and insecticides. Associations of the CYP2C19 genotype/phenotype with individual differences in drug efficacy (e.g. diazepam, omeprazole, proguanil) and toxicity (e.g. mephenytoin, barbiturates) have been documented by many investigators. At least 11 allelic variants of CYP2C19 gene were reported to date. Most of the mutant alleles found in the poor metabolizer (PM) led to the production of truncated and/or inactive proteins. Except for the exon 6, single-nucleotide mutations were reported in all nine exons of the gene. Genetic polymorphism of CYP2C19 shows marked interethnic variation with the population frequencies of PM phenotype ranging from 1~2% up to more than 50%. The prevalence of CYP2C19 PM tends to be higher in Asian and certain Pacific Islanders than other race or ethnic specificity. Genotyping results of CYP2C19 also revealed that there are different proportions of individual mutant alleles among ethnic populations. This may, in part, explains the interethnic difference in the metabolism of certain drugs (i.e. diazepam), though they were from the same CYP2C19 phenotype. Recently, our research group has studied the genotype and phenotype of CYP2C19 and found that the PM frequency (7~8%) in Thais is lower than other Asian populations. Molecular and clinical impacts of this finding warrant to further investigation.*

Key Words *: Cytochrome P450, CYP2C19, Genetic Polymorphism, Ethnic*

I. INTRODUCTION

One of the major causes of interethnic and individual variation in drug response is genetic polymorphism of drug metabolism. Such variation ranges from therapeutic failure to drug-induced toxicity, susceptibility to diseases, and drug-drug interactions when multiple drugs are taken concomitantly. It is now well described that polymorphisms are generated by mutations in the genes, which lead to either increase, decrease or absent of enzyme expression and activity by multiple molecular mechanisms. Among the most widely study of polymorphic drug metabolizing enzymes are those responsible for drug oxidations (i.e. cytochrome P450s, CYP2D6, CYP2C9, CYP2C19) and conjugations (N-acetyltransferase, NAT; thiopurine methyltransferase, TPMT).

This paper provides a brief and update review with focussing on the characterization and polymorphic variation of CYP2C19 among different ethnic populations. Its clinical and toxicological implications in relation to therapeutic drugs will also be discussed. Readers who want more additional information regarding this topic, are referred to the excellent articles by those authors (Sohn *et al.*, 1994; Bertilsson 1995).

II. MOLECULAR MECHANISM OF POLYMORPHISM

CYP2C19 is a member of the multi-family cytochrome P450 (CYP) enzyme (Nelson *et al.*, 1996). A polymorphism of this enzyme was initially revealed during clinical trials, by the discovery of deficient 4-hydroxylation of mephenytoin, a now rarely used antiepileptic drug, in human volunteers (Kupfer *et al.*, 1984). Although mephenytoin is commercially avail-

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Abbreviation: CYP: cytochrome P450, PM: poor metabolizer, EM: extensive metabolizer

able as a racemic mixture of *R*- and *S*-enantiomers, the hydroxylated deficiency is restricted to one of the two main metabolic pathways of disposition, namely stereoselective hydroxylation of S-mephenytoin in the *p*-phenyl position to 4-OH-mephenytoin. The enzyme, therefore, was originally named as *S*-mephenytoin hydroxylase before it was shown that the enzyme is closely related to other genes of the CYP2C subfamily and has later been designated as CYP2C19 (Goldstein *et al.*, 1994). Since then, CYP2C19 polymorphism had received considerable attention and been investigated by number of scientists. It is now known that CYP2C19 can play a pivotal role in catalyzing not only the S-mephenytoin, but also a number of drugs and chemicals as shown in Table 1.

Early studies in human liver microsomes from extensive metabolizer (EM) and poor metabolizer (PM) of S-mephenytoin suggested the deficiency of the drug-catalyzed enzyme. Cloning studies and immunoblots using an antibody raised against the purified protein, had confirmed the absent of CYP2C19 in those liver microsomes prepared from PMs. The deficiency is inherited as an autosomal recessive trait (Ward *et al.*, 1987) and is distinct from other CYP polymorphisms. The complete *CYP2C19* gene, together with other human *CYP2C* cluster, locates on chromosome 10q24, has been isolated and are ~55 kb in size (Gray *et al.*, 1995). The gene consists of nine exons and encodes for 490 amino acid sequences.

Table 1. A list of selected chemicals which are substrates of CYP2C19

CNS drugs	**Cardiovascular drugs**
Amitriptyline	Bufuralol
Citalopram	Metoprolol
Clomipramine	Propranolol
Clormethiazole	Verapamil
Clorzapine	Warfarin
Diazepam	**Gastrointestinal drugs**
Flunitrazepam	Cisapride
Hexobarbital	Lansoprazole
Imipramine	Omeprazole
S-Mephenytoin	Pantoprazole
Mephobarbital	Rabeprazole
Nordiazepam	**Sex hormones**
Nortriptyline	Desogestrel
Sertraline	Progesterone
Temazepam	Testosterone
Venfalaxine	**Miscellaneous**
Antimicrobial agents	Aminopyrine
Nelfinavir mesylate	Clarisoprodol
Pentamidine	Diallyl disulfide
Proguanil	Diclofenac
Zidovudine	Methadone
Insecticides	Tetrahydrocannabinol
Methoxyclor	Tolbutamide

To date at least 11 alleles of *CYP2C19* have been elucidated. There are two nomenclature systems for the polymorphic *CYP2C19* alleles. A trivial system, popularly used by several investigators, provides an abbreviated subscript (using small letters) to the gene such as 'wt' for *'wild-type'* and 'm1', 'm2', etc. for other *mutant* alleles. On the other hand, the expert nomenclature system prefers a prefix of '*' follows by an Arabic number to different alleles. For example, the *'wild-type'*, allele is named *CYP2C19*1* and the following *mutant* alleles founded are designated *CYP2C19*2, CYP2C19*3,* .. in this latter system. It is worth mentioned that all of the mutant *CYP2C19* alleles lead to either decrease or absent of enzyme activity, whereas the genetic polymorphism of other CYP enzymes, i.e. CYP2D6, may lead to either increase, decrease or absent of activity. So far, no gene duplication of CYP2C19 has been reported in human. Details of *CYP2C19* alleles are as the following and are summarized in Table 2.

*CYP2C19*1A* and *CYP2C19*1B* are the most abundant (wild-type) alleles found in human population. *CYP2C19*1B* differs from *CYP2C19*1A* in nucleotide position 99 (C→T) in exon 1. However, this is a silent mutation, and both alleles are still able to express the active CYP2C19 enzyme as in EM population.

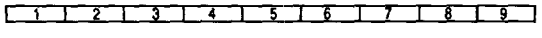
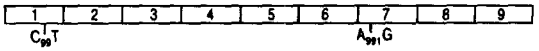
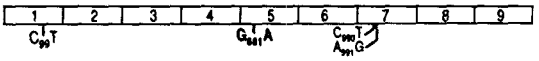
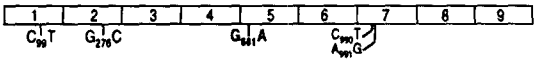
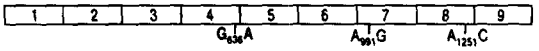
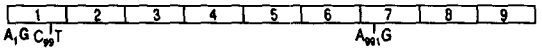
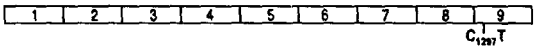
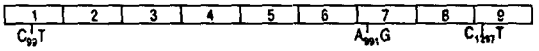
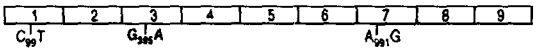
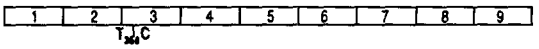
*CYP2C19*2* or *CYP2C19m1* is a mutant allele caused by G→A mutation at the nucleotide position 681 in exon 5. This creates an aberrant splice site and produced premature stop codon, which made a shortened form of CYP2C19 enzyme. The enzyme with 234 amino acid (~47% of wild-type) lacked the heam binding region and expressed inactive CYP2C19.

*CYP2C19*3* or *CYP2C19m2* is a second mutant found. Again, this G→A mutation led to a premature stop codon, but at the different nucleotide position of 636 in exon 4. This allele was reported with more frequency of occurrence in oriental population.

*CYP2C19*4* or *CYP2C19m3* is a mutant at the initiation codon from (ATG→GTG) which made no enzyme production.

*CYP2C19*5* or *CYP2C19m4* is a novel mutant form with C→T transition at the position of 1297 of exon 9 (Ibeanu *et al.*, 1998a). This lead to production of amino acid Arg→Trp in the heam binding region and

Table 2. Molecular mechanisms of mutation reported in CYP2C19 allelic variants

Allele	Trivial Name	Effect of Nucleotide Changes	Enzyme Activity	0 200 400 600 800 1000 1200 1400 1600 bp
CYP2C19*1A	$CYP2C19_{Wt1}$		Active	
CYP2C19*1B	$CYP2C19_{Wt2}$	$Ile_{311}Val$	Active	
CYP2C19*2A	$CYP2C19_{m1A}$	Splicing Defect	Inactive	
CYP2C19*2B	$CYP2C19_{m1B}$	Glu92 Asp Splicing defect	Inactive	
CYP2C19*3	$CYP2C19_{m2}$	Stop Codon	Inactive	
CYP2C19*4	$CYP2C19_{m3}$	GTG Initiation Codon	Inactive	
CYP2C19*5A	$CYP2C19_{m4}$ $CYP2C19_{TRP433}$	$Arg_{433}Trp$	Inactive	
CYP2C19*5B		$Ile_{331}Val$; $Arg_{433}Trp$	Inactive	
CYP2C19*6	$CYP2C19_{m5}$	$Arg_{132}Gln$; $Ile_{331}Vel$	Inactive	
CYP2C19*7	$CYP2C19_{m6}$	T to A base transversion at donor site of intron 5 (Exon Skipping)	Inactive	
CYP2C19*8		$Trp_{120}Arg$	Decrease	

inactive enzyme.

*CYP2C19*6* or *CYP2C19m5* is another form with G→A mutation at the position of 395 of exon 3 (Ibeanu *et al.*, 1998b). It was discovered in Swiss PM population.

*CYP2C19*7* or *CYP2C19m6* was reported in PM of Denmark (Ibeanu *et al.*, 1999). The T→A mutation occurred in the donor site, 5', of intron 5 and made gene dysfunction.

*CYP2C19*8* or *CYP2C19m7* is the most recently found in French PM with T→C mutation in the position of 358 of exon 3. (Ibeanu *et al.*, 1999).

In Asian PM populations, the genotype *CYP2C19*2* (*m1*) and *CYP2C19*3* (*m2*) cover nearly almost all of the mutant alleles. On the other hand both alleles can cover only up to 85% of PM in Caucasians. The other genotypes found in Caucasian PM are *CYP2C19*4* (3%) and *CYP2C19*5B* (1~5%), whereas this two latter alleles are rarely found in Chinese population. The rest mutant alleles have been reported with much lower frequency. It appears that there are possibly other mutants of *CYP2C19* to be discovered in the future, particularly in the Caucasian population.

III. PHENOTYPING AND GENOTYPING

Since the discovery of CYP2C19 polymorphism several methods had been developed to find precise and accurate means of describing or predicting individual CYP2C19 activity. Despite this enormous effort, there is currently limited consensus as to the most suitable method of characterizing this enzyme activity.

The initial method of describing CYP2C19 activity is 'phenotyping', where the individual metabolism of a suitable chemical probe is used to determine the enzyme activity primarily involved in its metabolism. Although it is often a tedious work and relies on many metabolic assumptions, phenotyping provides the most clinical relevant information and reflects of the interaction effects of genetic, environment and intrinsic factors on current CYP219 activity. To date, at least three chemical probes have been using widely for CYP219 phenotyping, the details of each probe will be summarized as the following.

1. Mephenytoin phenotyping

The racemate mephenytoin undergoes different me-

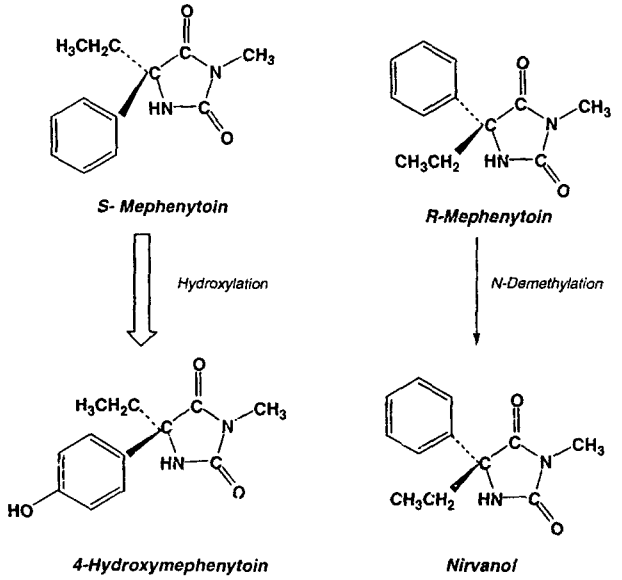


Fig. 1. Metabolic pathways of mephenytoin relevant to phenotyping for CYP2C19.

tabolic pathways in human. The *R*-form is mainly demethylated to nirvanol, which is slowly excreted, whereas the *S*-form is rapidly hydroxylated to give the excreted metabolite, 4-hydroxymephenytoin (Fig. 1). The latter pathway is mediated by CYP2C19 as the formation of 4-hydroxymephenytoin highly correlates with the enzyme content present in human liver microsomes (Goldstein *et al.*, 1994; Lasker *et al.*, 1998). There are a few methods of phenotyping CYP2C19 using mephenytoin. The first method measures the ratio of unchanged S-mephenytoin to *R*-mephenytoin. In CYP2C19 EM population this S/R ratio is low (less than 0.6), but the ratio is close to 1 in PM population as the result of lacking stereoselective metabolism of the *S*-mephenytoin. The second method uses the urinary hydroxylation index (HI) defined as the following, and high values of HI indicate the CYP2C19 PM population.

$$HI=\frac{\mu mol\ S\text{-mephenytion dose}}{\mu mol\ 4\text{-hydroxymephenytoin in vrine in } 0\sim 8\ hr}$$

However, phenotyping with mephenytoin is not without problem. The drug, develop for treatment of epilepsy, has never been popular because of many potential side effects. Lower dose (i.e. 50 mg) of mephenytoin is recommended by some investigators. This lead to a more difficult assay as undetectable amount of *S*-mephenytoin may be found in many urine samples. Furthermore, the stability problem of the drug in urine may interfere the precise differentiate of PM and EM.

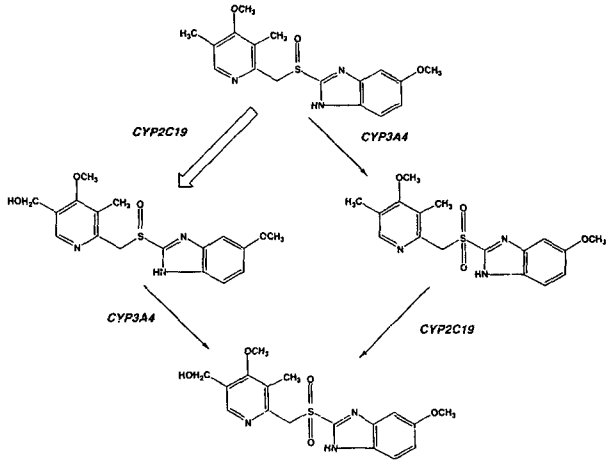


Fig. 2. Metabolic pathways of omeprazole relevant to phenotyping for CYP2C19.

2. Omeprazole phenotyping

This benzimidazole drug used for treatment of peptic ulcer has increasingly been popularity for phenotyping CYP2C19. Following administration of omeprazole, most of the drug is metabolized in the liver to 5'-hydroxyomeprazole and omeprazole sulfone. Both metabolites and other secondary metabolites are further excreted into the urine sulphone (Andersson *et al.*, 1990; 1994). The primary enzyme responsible for omeprazole hydroxylation is proven to be CYP2C19 (Fig. 2), as the amount of this enzyme in human liver microsomes correlated significantly with omeprazole hydroxylation (Lasker *et al.*, 1998).

For CYP2C19 phenotyping, the omeprazole serum metabolite ratio (MR) is defined by the ratio of the concentration of omeprazole to 5'-hydroxyomeprazole. Appropriate sampling time is between 1~3 hr post oral ingestion. However, in some individual with unexplained absorption pattern, the 2 hr concentration of either drug may not be found, therefore 3 hr blood sample appears to be a better choice for any single assay. Unlike the mephenytoin, urine sample is not appropriate for phenotyping with omeprazole due to very small amount of 5'-hydroxyomeprazole is excreted via this route.

3. Proguanil phenotyping

The antimalarial agent, proguanil, has also been

used as a test probe for CYP2C19. *In vivo* studies has found that the primary oxidation and cyclization of the drug to form cycloguanide is impaired in CYP2C19 PM (Ward *et al.*, 1991; Brosen *et al.*, 1993). *In vitro* study has also confirmed the catalytic involvement of CYP2C19 as this rate of this reaction was significantly correlated with other CYP2C19 indices such as omeparazole hydroxylation (Birkett *et al.*, 1994). Unfortunately, the role of other enzyme likes CYP3A has been found in the same reaction, although CYP3A4 appears to be the low affinity enzyme responsible for the cycloguanide formation (Funck-Brentano *et al.*, 1997).

The urinary concentration ratio of the cycloguanide to proguanil (CG/PG) is recommended for CYP2C19 phenotyping as it is linearized to proguanil clearance via cycloguanide formation (Somogyi *et al.*, 1997). However, this ratio may not able to completely differentiate the CYP2C19 PM and EM as some studies have found no correlation between this ratio and the mephenytoin HI (Partovian *et al.*, 1995; Funck-Brentano *et al.*, 1997).

4. Genotyping

With modern molecular biology techniques, *CYP2C19* gene can be characterized with only a single venous blood sampling. The 'genotyping' study has many advantages such as minimized ethical problems, rapid turnaround time, and can be done in large population with reasonable cost. The genotyping for the most two common mutations of *CYP2C19*2* and *CYP2C19*3* used the restriction fragment length-polymerase chain reaction (RFLP) analysis. By using specific primers designed for the exon 5 and 4, the sampling genes can be analyzed for *CYP2C19*2* and *CYP2C19*3* respectively (Goldstein and Blaisdell, 1996). After successive digestion of the amplified DNA with appropriate restriction endonuclease, the result can be then analyzed using the electrophoresis and ethidium bromide staining as shown in Fig. 1. In the analysis of *CYP2C19*2*, the DNA product from homologous *CYP2C19*2/*2* is not cut by *SmaI* digestion and shows only single DNA band of at 321 bp size. In contrast, the homologous wild type of *CYP2C19*1/*1* (*CYP2C19wt*) exhibits double DNA bands at 109 and 212 bp. Heterologous *CYP2C19*1/*2* shows three DNA bands of 109 212 and 321 bp. The same analogy can apply for the analysis of *CYP2C19*3* with the aid of *BamH1* digestion.

Genotyping still has limitations as discrepancy between genotype and phenotype may occur in some individual. It is of clinical relevant only to the degree of predicting the enzyme expression or phenotype. In certain patients like those with hepatic diseases or advance cancer, decrease in enzyme activity may result in a discordance between genotype and phenotype (Adedoyin *et al.*, 1998; Williams *et al.*, 2000).

5. Interethnic variations

From the beginning of the study of S-mephenytoin hydroxylase or CYP2C19 genetic polymorphism, it appears that the incidence of CYP2C19 PM vary significantly among the three large races, i.e. Asians (Mongoloids), Caucasians and Africans (Negroids). Shortly after the discovery of this enzyme, there were trends in findings that higher incidence (3-fold to 6-folds) of PMs in Asians than in Caucasians (Nakamura *et al.*, 1985; Jurima *et al.*, 1985).

Several studies have been showed that about 1~6% of Caucasians are PMs of CYP2C19 (Table 3). Marked differences of PM frequency are found either in inter- and intra-ethnic Caucasians populations. Furthermore, it is not unusual to find different estimation when using different studying methods. For example, the studies in Turkish volunteer using mephenytoin, proguanil and omeprazole, reported observed frequencies of PM as 0.9%, 5.6%, and 7.7%, respectively (Basci *et al.*, 1994, 1996; Kortunay *et al.*, 1997). Using genotyping method and larger number of volunteer, the frequency of CYP2C19 PM in this population is lately predicted as 1% (Aynacioglu *et al.*, 1999).

It is, therefore, not easy to estimate a true PM incidence of any populations among several uncertainties. Because of the limited number of volunteer participated and differences in probing method used, a new approach of meta-analysis has recently been employed. This method makes use of a systemic structured overview of studies that synthesize and integrate information across previous available data on the selected ethnic populations. Based on the pooled data from 22 studies (n=3,990), the overall preva-

Table 3. Interethnic differences in the frequencies of poor metabolizer of CYP2C19

Ethnic group	Frequencies of PM (%)	n	Method used*	References
Asians of:				
China	14	1,117	Meta-analysis	Xie *et al.*, 1996
India (north)	12	200	OM	Lamba *et al.*, 2000
Indonesia	15	104	MP	Setiabudy *et al.*, 1994
Japan	14	223	RFLP	Tsuneoka *et al.*, 1996
Korea	13	103	OM	Roh *et al.*, 1996
Philipines	23	52	MP	Goldstein *et al.*, 1997
Sri Lanka (Sinhalese)	14	111	MP	Weerasuriya *et al.*, 1994
Thailand	18	170	PG	Edstein *et al.*, 1994
Vietnam	22	37	MP	Brosen *et al.*, 1993
Mid-East Asians of :				
Isarael	3	140	MP	Sviri *et al.*, 1999
Saudi Arabians	2	97	MP	Goldstein *et al.*, 1997
Caucasians of :				
Canada	4	113	MP	Jurima *et al.*, 1985
Denmark	3	241	RFLP	Bathum *et al.*, 1998
England	2	137	PG	Helsby *et al.*, 1990
France	6	132	MP	Jacqz *et al.*, 1988
German	4	174	MP	Brockmoller *et al.*, 1995
Greenland	3-9	471	MP	Clasen *et al.*, 1991
Netherland	2	4,301	MP	Tamminga *et al.*, 1999
Portugal	1	153	RFLP	Ruas & Lechner, 1997
Russia	2	218	MP	Marandi *et al.*, 1997
Spain	1	373	MP	Reviriego *et al.*, 1993
Sweden	3	488	MP	Bertilsson *et al.*, 1992
Switzerland	5	221	MP	Kupfer & Preisig, 1984
Turkey	1	404	RFLP	Aynacioglu *et al.*, 1999
USA	3	122	MP	Balian *et al.*, 1995
Africans of:				
Ethiopia	5	114	MP	Persson *et al.*, 1996
Tanzania (Bantu)	7	251	MP, OM	Herrlin *et al.*, 1998
Zimbabwe (Shona)	4	103	MP	Masimirembwa *et al.*, 1995
Micellaneous:				
Inuit (Canadian)	2	152	MP	Jurima-Romet *et al.*, 1996
Vanuatu	61	5,538	RFLP	Kaneko *et al.*, 1997; 1999

*Method: MP=mephenytoin phenotyping; OM=omeprazole phenotyping; PG=proguanil phenotyping; RFLP=restriction-fragment length polymorphism.

lence of CYP2C19 PM was estimated to be 2.8% of Caucasians (Xie *et al.*, 1999a). In the same study, the observed frequencies of *CYP2C19* genotypes were 73% for homologous *CYP2C19*1* (wt/wt), 26% for heterologous *CYP2C19*1/*2* or **1/*3*, and 2.1% for homologous *CYP2C19*2/*2*. However, a considerable proportion of Caucasian PM subjects (10% of defective alleles) were not elucidated for their genotypes, suggesting that there are novel *CYP2C19* genotypes to be found in the future.

The next major race, which has been intensively investigated for its CYP2C19 polymorphism, is the Asian populations. In fact, the effect of CYP2C19 deficiency would be more pronounce in Asians than other racial populations. This population exhibits its diverse heterogeneity across worldwide geographical settlements. To date, the most informative data on CYP2C19 polymorphism of Asians are probably gathered from those of the Far East, i.e. the Chinese, Korean and Japanese populations. Recent meta-analyses of CYP2C19 polymorphism using primary data from both phenotyping and genotyping studies have estimated the Chinese PMs of 14% (Xie *et al.*, 1996; Xie, 2000). Nearly the same incidence (13%) of PM was also reported in the Korean populations using either mephenytoin or omeprazole phenotyping method (Roh *et al.*, 1996). For these Korean PMs, the mutant *CYP2C19* genes found are the homozygous *CYP2C19*2/*2*, heterologous *CYP2C19*2/*3* and homozygous *CYP2C19*3/*3*, by which the allele frequencies of *CYP2C19*2* and **3* are 21% and 12%, respectively.

It appears that the frequencies of CYP2C19 PM in Southeast Asians (15~23%) tend to be higher than those of the Far East. These results often obtained from limited number of individual studied, and in some case using selected populations that might be not well representative of their homeland populations (Brosen *et al.*, 1993). In some diverse populated

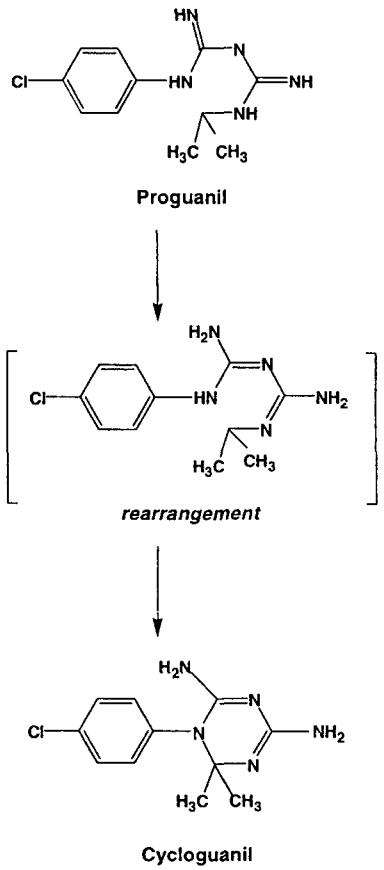


Fig. 3. Metabolic pathways of proguanil relevant to phenotyping for CYP2C19.

country like Indonesia, the possibility of genetic heterogeneity of populations may exist. For Thai populations, the initial work on CYP2C19 polymorphism using proguanil had found the incidence of PM of 18% (Edstein *et al.*, 1994). However, our recent work using omeprazole as a test probe has revealed only half value, i.e. 8% of Thai PMs. (Tawalee *et al.*, 1999). Whether this discrepancy reflects a true heterogeneity of Thai populations or derives from the different methodology used warrant further investigation in a larger number of volunteer.

There are few studies of CYP2C19 polymorphism among African descents, albeit the diverse nature of this ethnic populations. Although, genetic distances of the African population has been proposed to separate from Caucasians and Asians (Mongoloids) since 150,000 years ago (Nei and Saitou, 1986), the frequencies of PMs in this population are only slightly higher than those of the Caucasians. Again, using meta-analysis approach, The PM frequency among African descents derived from 7 studies, were estimated to be 3.9% (Xie *et al.*, 1999b). The observed alleles of *CYP2C19*1*, *CYP2C19*2* and *CYP2C19*3* were 82.3%, 17.3% and 0.4%, respectively.

IV. CLINICAL AND TOXICOLOGICAL IMPLICATIONS

As shown by the diverse list of CYP2C19 substrates (Table 1), they could be bases, acids or neutral drugs. One might predict a lower metabolic rate and/or clearance of those drugs in PM populations. Evidence have been provided to support this hypothesis across interethnic populations for many drugs including diazepam (Zang *et al.*, 1990), omeprazole (Caraco *et al.*, 1996), and phenobarbitone (Mamiya *et al.*, 2000). However, for several CYP2C19 substrates, this information is of limited usefulness as they are also metabolized by other enzymatic pathways, thus one single enzyme contributes little to the total drug clearance in the body. To review the whole list of substrate is beyond the scope of this review, therefore, we will select only recent findings that have demonstrated the relevant of CYP2C19 polymorphism to clinical and toxicological implications.

Apart from the higher risk of sedation when taken mephenytoin, it was also demonstrated that CYP2C19 PM metabolized carisoprodol slower than EM volunteer, and had an increased risk of adverse drug events, particularly the *Type A* (concentration-dependent) reactions (Dalen *et al.*, 1996). These effects included drowsiness and hypotension, even when treated with usual doses of carisoprodol. Furthermore, several *in vitro* studies have shown that a number of clinically used drugs including the antiplatelet drug, ticlopidine (Ki=1.2 μM) and the antihistamine, loratadine (Ki=0.17 μM), can markedly inhibit CYP2C19 activity (Nicolas *et al.*, 1999; Ko *et al.*, 2000). Since the molar concentrations of inhibition of these drugs are in the therapeutic range, the potential *in vivo* interactions of the drugs with CYP2C19 warrant additional investigations before any clinical significance can be concluded. It is worth mentioned that a group of expert on adverse drug reactions monitoring has recently reported that individual possessed the CYP2C19*2 appears to be a risk factor for cardiotoxicity of terodiline (Ford *et al.*, 2000). This finding has interest-

ingly made use of a relationship between epidemiological (the UK's *yellow card system*) and genetically analysis data.

Omeprazole together with antimicrobial drug is now a regimen of choice for treatment of peptic ulcer with *Helicobacter pyroli* infection. Mutual drug interactions between omeprazole and the macrolide clarithromycin, which lead to increase plasma concentration of each drug, has been reported (Furuta *et al.*, 1999). Moreover, there were significant differences in these changes among the three *CYP2C19* genotypes, i.e. homozygous EMs, heterologous EMs and PMs, which implied the *CYP2C19* gene dosing effects on the drugs used. Recent findings in Japanese patients have revealed that cure rate of CYP2C19 PM were higher than those who carried either homozygous or heterozygous CYP2C19 EM (Aoyama *et al.*, 1999). On the other hand, an EM patient appears to need a high dose of omeprazole (2-3 fold) to cure of her refractory duodenal ulcer (Furuta *et al.*, 2000). These clinical findings demonstrate that the pharmacological effect of omeprazole on intragastric pH depend on CYP2C19 expression. Thus, the genotyping test of *CYP2C19* should be proven useful for an optimal prescription of omeprazole to individual patient.

There are a few population studies to test whether the genotype of CYPs could contribute to longevity. A higher frequency of CYP2C19 PM phenotype (18.5%) was reported in elderly African descents living in Pittsburgh (Pollock *et al.*, 1991), despite, the limit number of volunteer studied and had not been confirmed by later studies in this population. In contrast, a more recent study showed that frequency of CYP2D6 PM was higher in the aged Danish population but not with CYP2C19 PM (Bathum *et al.*, 1998). This finding is ratified in another population study by which no significant difference in the frequency of CYP2C19 PM between the elderly and young Swedish (Yamada *et al.*, 1998).

ACKNOWLEDGEMENTS

We sincerely thanks Ms Arporn Tawalee, for her assistance and contribution with genotyping and omeprazole assay, Dr Palarp Sinhasenee, the president of the Toxicological Society of Thailand, for her supporting to the ASIATOX II meeting.

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