**DRUG DISPOSITION**

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# Clinical Significance of the Cytochrome P450 2C19 Genetic Polymorphism

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## Abstract

Cytochrome P450 2C19 (CYP2C19) is the main (or partial) cause for large differences in the pharmacokinetics of a number of clinically important drugs. On the basis of their ability to metabolise (*S*)-mephenytoin or other CYP2C19 substrates, individuals can be classified as extensive metabolisers (EMs) or poor metabolisers (PMs). Eight variant alleles (CYP2C19*2 to CYP2C19*8) that pre-

dict PMs have been identified. The distribution of EM and PM genotypes and phenotypes shows wide interethnic differences. Nongenetic factors such as enzyme inhibition and induction, old age and liver cirrhosis can also modulate CYP2C19 activity.

In EMs, ~80% of doses of the proton pump inhibitors (PPIs) omeprazole, lansoprazole and pantoprazole seem to be cleared by CYP2C19, whereas CYP3A is more important in PMs. Five-fold higher exposure to these drugs is observed in PMs than in EMs of CYP2C19, and further increases occur during inhibition of CYP3A-catalysed alternative metabolic pathways in PMs. As a result, PMs of CYP2C19 experience more effective acid suppression and better healing of duodenal and gastric ulcers during treatment with omeprazole and lansoprazole compared with EMs. The pharmacoeconomic value of CYP2C19 genotyping remains unclear. Our calculations suggest that genotyping for CYP2C19 could save approximately $US5000 for every 100 Asians tested, but none for Caucasian patients. Nevertheless, genotyping for the common alleles of CYP2C19 before initiating PPIs for the treatment of reflux disease and *H. pylori* infection is a cost effective tool to determine appropriate duration of treatment and dosage regimens. Altered CYP2C19 activity does not seem to increase the risk for adverse drug reactions/interactions of PPIs.

Phenytoin plasma concentrations and toxicity have been shown to increase in patients taking inhibitors of CYP2C19 or who have variant alleles and, because of its narrow therapeutic range, genotyping of CYP2C19 in addition to CYP2C9 may be needed to optimise the dosage of phenytoin. Increased risk of toxicity of tricyclic antidepressants is likely in patients whose CYP2C19 and/or CYP2D6 activities are diminished. CYP2C19 is a major enzyme in proguanil activation to cycloguanil, but there are no clinical data that suggest that PMs of CYP2C19 are at a greater risk for failure of malaria prophylaxis or treatment. Diazepam clearance is clearly diminished in PMs or when inhibitors of CYP2C19 are coprescribed, but the clinical consequences are generally minimal.

Finally, many studies have attempted to identify relationships between CYP2C19 genotype and phenotype and susceptibility to xenobiotic-induced disease, but none of these are compelling.

The initial discovery of the first poor metaboliser (PM) of mephenytoin at Vanderbilt University in 1979,[1] and the subsequent demonstration of the genetic basis for this phenotype,[2,3] have spurred extensive research into the genetic basis for the interindividual variations of (*S*)-mephenytoin 4′-hydroxylation and the role of this enzyme in drug metabolism. Studies conducted by Wrighton et al.[4] and by Goldstein et al.[5] have clearly demonstrated that the (*S*)-mephenytoin hydroxylase is cytochrome P450 2C19 (CYP2C19). Based on their ability to metabolise (*S*)-mephenytoin or other probe drugs, most of the population throughout the world can be categorised as extensive metabolisers (EMs) and PMs. A wealth of research has been performed into the molecular genetic basis of the *CYP2C19* polymorphism and the enzymology of the proteins expressed from it. Seven alleles of the *CYP2C19* gene have been so far identified that successfully predict PMs of CYP2C19. Both genotypic and phenotypic data indicate marked ethnic variation in the frequency of PMs of CYP2C19. Due to the development of specific *in vitro* and *in vivo* tools to characterise CYP2C19, it is now known that this enzyme is involved in the metabolism (and thus is the cause for the wide interindividual and ethnic variation in the pharmacokinetics) of several frequently prescribed drugs. Reliable phenotyping and genotyping tools are available for screening CYP2C19 ac-

tivity in patients, but the clinical relevance of this enzyme and of the genetic polymorphism in its expression is not readily apparent to most practising physicians. Neither genetic nor phenotypic testing for CYP2C19 activity is routinely used in clinical practice to design appropriate therapeutic regimens and improve the outcome of treatment with CYP2C19 substrate drugs. This article is an extensive review of published data in the context of the clinical relevance of CYP2C19 genetic polymorphism. Our goal is to evaluate the case for routine clinical genetic testing: the potential value that may be derived from it and the attendant costs and risks.

The anticonvulsant mephenytoin was the first effective probe drug that was able to discriminate the two different phenotypes (EMs and PMs) of the genetic polymorphism now known to be due to variation in CYP2C19 expression, and it remains the most specific. Mephenytoin exists as a racemic mixture of two optically active enantiomers: the (*R*)- and (*S*)- forms. An early pharmacokinetic study of mephenytoin in dogs indicated that the elimination of mephenytoin is stereoselective.[6] During a study to confirm the stereoselective metabolism of mephenytoin in humans, Dr. Adrian Kupfer and coworkers at Vanderbilt University noted one patient who experienced extreme sedation after taking mephenytoin 300 mg/day for 5 days and for that reason terminated the study. The effect was subsequently shown to be due to deficiency of mephenytoin hydroxylation, thus marking the discovery of the first PM of mephenytoin.[1,7] Their studies,[1,7] and other subsequent clinical trials[8-10] have demonstrated that the elimination of (*S*)-mephenytoin in humans is significantly faster, due to rapid 4′-hydroxylation, than that of (*R*)-mephenytoin, which undergoes slow *N*-demethylation to nirvanol. This stereoselective metabolism of mephenytoin (*S*-/*R*-mephenytoin ratio) has been successfully exploited to test for the defect in *S*-mephenytoin 4′-hydroxylation and to demonstrate that this deficiency was familial.[1,8,9,11] Subsequent studies have shown that CYP2C19 is involved in the metabolism of several clinically useful drugs other than (*S*)-mephenytoin and that genetic polymorphism of this enzyme is the main cause for wide interindividual/interethnic variation in the pharmacokinetics of several clinically important medications. These studies have been reviewed several times over the years.[12-19]

Which drugs metabolised by CYP2C19 are most likely to confer clinical importance on the genetic polymorphism? The variety and usefulness of drugs metabolised by CYP2C19 suggest that there will be important clinical implications for both EM and PM genotypes. Particularly, drugs for 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. The potential clinical relevance of CYP2C19 genetic polymorphism to the safety and therapeutic efficacy of drugs has received attention recently through studies that have shown increased effectiveness of proton pump inhibitors (PPIs) such as omeprazole in the treatment of *Helicobacter pylori* infections and reflux disease and increased toxicity of substrate drugs (e.g. phenytoin and tricyclic antidepressants) in PMs of CYP2C19 or during drug interactions. These data suggest that genotyping of CYP2C19 might be a useful means of predicting clinical efficacy and adverse drug reactions or interactions of CYP2C19 substrate drugs, but no pharmacogenetic test has been approved by the US Food and Drug Administration as of the year 2002, despite the availability of simple tests for a number of genetically polymorphic cytochrome P450 isoforms, thiopurine methyltransferase and a number of other important enzymes, transporters and receptors.

Genetic polymorphism also influences the way nongenetic factors (e.g. drug interactions, age and disease conditions) modulate the activity of CYP2C19. Some CYP2C19 substrates are potent inhibitors of the CYP system, and increased plasma concentrations of these drugs in genetic PMs of CYP2C19 may increase the likelihood of non–CYP2C19-mediated drug interactions. Knowledge of all factors that control the expression (activity)

of CYP2C19 is important to identify and predict the pharmacokinetic changes and the resulting pharmacodynamic response to CYP2C19 substrates and thus evaluate the feasibility of genetic testing.

## 1. Factors Affecting Expression and Activity of Cytochrome P450 (CYP) 2C19

### 1.1 Genetic Polymorphism

#### *1.1.1 Gene Structure and Sites of Polymorphism*

The high interindividual and interethnic variability in the pharmacokinetics of CYP2C19 substrates is mostly understood in terms of the genetic polymorphism of this enzyme. The evidence provided by Kupfer and his coworkers[8] that the deficiency in (*S*)-mephenytoin hydroxylation may be monogenic has stimulated research into its mode of transmission and genetic variations responsible. Key in this respect was the work of Wrighton et al.[4] in 1993, who provided the first evidence that (*S*)-mephenytoin 4′-hydroxylase is CYP2C19, a finding that was further confirmed by Goldstein et al.,[5] who cloned the individual CYP2C enzymes and tested their activity toward stereoselective metabolism of (*S*)-mephenytoin *in vitro*. CYP2C19 is a protein of 490 amino acids encoded by the *CYP2C19* gene, which has nine exons[20] and is mapped to chromosome 10 (10q24.1-q24.3).[21] CYP2C19 protein is mainly present in the liver, but a significant activity (0.8 to 13.1 pmol/min/mg of protein) has also been identified in the gut wall.[22]

Seven genetic variant alleles responsible for the majority of the enzymatic deficiency associated with PMs of (*S*)-mephenytoin have been so far identified. Work in the laboratory of de Morais and Goldstein identified two genetic defects in CYP2C19[2,23] that are responsible for the majority of the PMs of this enzyme (table I). These variants are two null alleles, which include a splice defect in exon 5 (*CYP2C19*2*; trivial name, m1; single base change G→A)[2] and a premature stop codon at position 636 of exon 4 (*CYP2C19*3*; trivial name, m2; single base change G→A),[23] while *CYP2C19*1* represents the wild-type allele. In both variants, a premature stop codon resulting in truncated and inactive enzyme or a truncated protein that is unable to bind to the haem moiety is produced. Several studies indicate that the distribution of these common alleles is different among different populations. For example, the frequency of *CYP2C19*2* has been reported to be ~17%, 30% and ~15% in African-Americans, Chinese and Caucasians, respectively, and the *CYP2C19*3* allele was shown to be more frequent in Chinese (~5%) than in Caucasians (0.04%) and Blacks (0.4%) [reviewed by Xie et al.[24]]. These two alleles account for almost all PMs in Asian and Black African populations. The main defective allele, *CYP2C19*2*, accounts for some 75 to 85% of

**Table I.** Alleles of *CYP2C19*, the gene for cytochrome P450 2C19, so far identified

| *CYP2C19* allele | Critical nucleoside change | Effect | Protein change | Enzyme activity | References |
|---|---|---|---|---|---|
| *1 | None | Wild type | | Normal | 20,26 |
| *2 | G681A point mutation in exon 5 | Splicing defect in exon 5 | Premature termination of protein synthesis | None | 2,27 |
| *3 | G636A single base transition | Premature stop codon | Truncated protein | None | 23,28 |
| *4 | $A_1 \rightarrow G$ | Mutation of initiation codon | Met→Val (inhibits translation) | None | 29 |
| *5 | C1297T transition | | Arg433→Trp | Markedly reduced | 30,31 |
| *6 | G395A transition in exon 3 | | Arg132→Gln | None | 27 |
| *7 | T→A inversion at 5′-splice site of intron 5 | Intron 5 splicing defect | | None | 32 |
| *8 | T358C transition on exon 3 | | Trp120→Arg substitution | Decreased | 32 |

CYP2C19 alleles responsible for PMs in Orientals and Caucasians.[2] Although *CYP2C19*3* is extremely rare in Caucasian populations, it accounts for almost all the remaining defective alleles in Orientals.[25]

Because the *CYP2C19*2* allele does not explain all PMs in Caucasians, investigators have suspected that additional variant alleles might exist and studies have revealed additional variant CYP2C19 alleles in Caucasian PMs (table I), which affect either expression of the protein or catalytic activity, identifying ~99.74% of defective alleles (reviewed by Wedlund[19]). These are: *CYP2C19*4* (a variant of the initiation codon),[29] *CYP2C19*5* (Arg433→Trp, affecting structure and stability),[30] *CYP2C19*6* (Arg132→Gln, affecting structure and stability),[27] *CYP2C19*7* (intron 5 splicing defect)[32] and *CYP2C19*8* (Trp120→Arg, affecting structure and stability).[32]

The *CYP2C19* gene structure and the sites of polymorphism so far identified are illustrated in table I. The variant alleles (*CYP2C19*2* to *CYP2C19*8*) explain almost all PMs of CYP2C19. Prediction of phenotype from genotype is a relatively simple task for CYP2C19, as the genotyping of an individual for any of these alleles reliably categorises them as PMs or EMs. Since the incidence of 'genetic outliers', i.e. patients who carry a nonfunctional allele that has not been indentified would appear to be <1%, CYP2C19 genotyping should be sensitive as well as specific. Simple genotyping tests are available for the two most frequent alleles (*CYP2C19*2* and *CYP2C19*3*), and so it is now possible to rapidly screen relatively large groups of patients or volunteers relatively quickly.

#### *1.1.2 Ethnic/Racial Distribution of the Poor Metaboliser Phenotype*

The poor metaboliser phenotype is inherited as an autosomal recessive trait and its distribution in a large number of populations has been studied. As indicated above, the activity of CYP2C19 *in vivo* can be assessed through the use of specific phenotypic probe drugs. Using these tools, two distinct groups of individuals are identifiable according to the extent to which they metabolise the probe under study. The majority in all populations studied are relatively fast or extensive metabolisers (EMs), whereas the minority are relatively slow or poor metabolisers (PMs).

The EM phenotypes consist of the homozygous and heterozygous genotypes for the wild-type alleles, and their frequency in the population depends on ethnicity. Although gene duplication has been reported for other CYPs (e.g. CYP2D6) in certain populations,[33] and the same has been suggested for CYP2C19 on the basis of omeprazole hydroxylation,[34] no gene duplication has so far been reported for CYP2C19. The large interindividual and interethnic variation in the metabolic activity within the EM phenotypes is therefore mostly due to a gene dose effect.

In 1985, two studies reported a much higher incidence (18 to 23%) of PMs of (*S*)-mephenytoin in Japanese than in Caucasians.[35,36] A similarly high incidence has been shown in Chinese (15 to 17%)[37] and in Koreans (13%).[38] Subsequent studies have used a combination of phenotyping and genotyping tests, and have confirmed marked interethnic variation in the frequency of the PM phenotype: there is a higher frequency of the trait in Asian (12 to 23%) than in Caucasian (1 to 6%),[15,17,25] or Black African (1 to 7.5%)[14] populations. The frequency of this phenotype in African, African-American and Arab populations appears to be similar to that in Caucasians.[14,17,34,39] The PM trait does not seem to be present in the Cuna Indians of Panama.[40] In contrast, on the island of Vanuatu in the Pacific Ocean, 79% of the population are PMs,[15,41] probably as the result of a genetic founder effect in this community. The distribution of CYP2C19 PMs in the wide range of different populations studied and the methods used to make the determination are summarised in table II.

This interethnic difference in the distribution of PM traits is the primary cause for the wide interethnic differences in the metabolism of CYP2C19 substrate drugs documented in the literature. The

**Table II.** Distribution of poor metabolisers (PM) of cytochrome P450 2C19 in various ethnic groups

| Ethnic group | Phenotype | | Genotype | | | |
|---|---|---|---|---|---|---|
| | probe | PM/total (%) | *2/*2 | *2/*3 | *3/*3 | PM/total (%) |
| **Asian/Oceanian** | | | | | | |
| Japanese[25] | MP-HI | 8/53 (15.1) | 3/53 (5.7) | 4/53 (7.5) | 1/53 (1.9) | 8/53 (15.1) |
| Japanese[42] | MP-HI | 7/46 (15.2) | 20/186 (10.8) | 12/186 (6.4) | 3/186 (1.6) | 35/186 (18.8) |
| Japanese[43] | MP-HI | 45/200 (22.5) | | | | |
| Japanese[35,44] | MP-S/R | 18/100 (18.0) | | | | |
| Korean[45] | OMP | 13/103 (12.6) | NA | NA | NA | 12/103 (11.7) |
| Korean[38] | MP-HI | 26/206 (12.6) | | | | |
| Filipinos[25] | MP-HI | 12/52 (23.1) | 7/52 (13.5) | 5/52 (9.6) | 0 | 12/52 (23.1) |
| Chinese[37] | MP-S/R | 20/137 (14.6) | | | | |
| Chinese[43] | MP-HI | 17/98 (17.4) | | | | |
| Chinese (Han)[31] | MP-S/R | 20/101 (19.8) | NA | NA | NA | 20/101 (19.8) |
| Chinese (Bai)[31] | MP-S/R | 27/202 (13.4) | NA | NA | NA | 27/202 (13.4)[a] |
| Chinese (Taiwanese)[25] | | | NA | NA | NA | 18/118 (15.0) |
| Sri Lanka (Sinhalese)[46] | MP-S/R | 16/111 (14.0) | | | | |
| Indian[47] | OMP | 11/100 (11.0) | | | | |
| Indian (north)[48] | MP-S/R | 10/48 (20.8) | | | | |
| Indonesian[49] | MP-HI | 16/104 (15.4) | | | | |
| Vietnamese (Denmark)[50] | MP-S/R | 8/37[19] | | | | |
| South Pacific Polynesian[51] | Proguanil | 8/59 (13.6) | | | | |
| Greenland[b] [52] | | | | | | |
| East (Dorset) | MP-S/R | 28/300 (9.3) | | | | |
| West (Inuit) | MP-S/R | 5/171 (2.9) | | | | |
| **Middle East** | | | | | | |
| Saudi Arabian[25] | MP-HI | 2/97 (2) | 2/97 (2) | 0 | 0 | 2/97 (2) |
| Turkish[53] | MP-S/R | 1/106 (0.94) | | | | |
| Jordanian[54] | MP-HI, S/R | 9/194 (4.6) | | | | |
| Jewish Israeli[55] | MP-S/R, HI | 4/140 (2.9) | 4/140 (2.9) | 0 | 0 | 4/140 (2.9) |
| **African** | | | | | | |
| Tanzanian (Bantu)[56] | MP-S/R, 8/251 (7.5) | 7/251 (2.8) | 1/251 (0.4) | 0 | 8/251 (3.2) | |
| Tanzanian[57] | OMP | 10/216 (4.6) | | | | |
| Zimbabwe (Shona)[58] | MP-S/R | 4/103 (4.0) | 3/103 (3.0) | 0 | 0 | 3/103 (3.0) |
| Ethiopian[59] | MP-S/R | 6/114 (5.2) | 3/114 (2.6) | 3/103 (2.6) | 0 | 6/103 (5.2) |
| **Caucasian-European** | | | | | | |
| Swedish[60] | | | 1/83 (1.2) | 0 | 0 | 1/83 (1.2) |
| Swedish[37] | OMP, MP-S/R | 7/160 (4.6) | 6/160 (3.8) | 0 | 0 | 6/160 (3.8) |
| Swedish[37] | MP-S/R | 16/488 (3.3) | | | | |
| Swedish[61] | MP-S/R | 7/253 (2.8) | | | | |
| French[62] | MP-HI | 8/132 (6.0) | | | | |
| Danish[63] | MP-S/R | 9/358 (2.5) | | | | |
| Danish[64] | | | 9/239 (3.8) | 0 | 0 | 9/239 (3.8) |
| Portuguese[65] | | | 2/153 (1.3) | 0 | 0 | 2/153 (1.3) |
| Spanish[66] | MP-S/R | 5/373 (1.3) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Russian (Estonia)[67] | MP-S/R | 5/218 (2.3) | | | | |
| Estonian[68] | MP-S/R | 2/210 (0.95) | | | | |
| Australian[69] | Proguanil | 7/99 (7.0) | 3/99 (3.0) | 0 | 0 | 3/99 (3.0) |
| **African-American** | | | | | | |
| USA (NC)[25] | | | 8/108 (7.0) | 0 | 0 | 8/108 (7.0) |
| USA (MO, KS?)[70] | OMP | 2/100 (2.0) | 2/100 (2.0) | 0 | 0 | 2/100 (2.0) |
| USA (PA?)[71] | | | 8/233 (3.4) | 0 | 0 | 8/233 (3.4) |
| USA (TN)[39] | MP-S/R | 2/191 (2.0) | 0 | 0 | 0 | 0/76 (0) |
| **Caucasian-American** | | | | | | |
| USA (NC)[25] | | | 2/105 (2.0) | 0 | 0 | 2/105 (2.0) |
| USA (TN)[35,44] | MP-S/R | 5/183 (2.7) | | | | |
| USA (TN)[72] | MP-S/R | 4/156 (2.6) | | | | |
| Canada (Toronto)[73] | MP-HI | 2/83 (2.4) | | | | |
| **Native-American, Australian** | | | | | | |
| Canadian Indian[74] | | | 22/115 (19.1) | 0 | 0 | 22/115 (19.1) |
| Canadian Inuit[75] | MP-S/R | 3/152 (2.0) | 3/152 (2.0) | 0 | 0 | 3/152 (2.0) |
| Cuna Indian (Panama)[40] | MP-HI | 0/96 (0) | | | | |
| Aborigines (Australia)[76] | | | 26/227 (11.5) | 26/227 (11.5) | 6/227 (2.6) | |

a Includes one PM with *2/*5 mutation.

b Inuit of West Greenland is mixed with Caucasian, while Dorset population of East Greenland is less mixed.

**MP-HI** = mephenytoin hydroxylation index; **MP-S/R** = *S*/*R*-mephenytoin ratio; **NA** = not available; **OMP** = omeprazole metabolic ratio.

following examples illustrate this possibility. Zhang et al.[77] compared the pharmacokinetics of diazepam in Chinese and Caucasian individuals and showed that the elimination of diazepam is slower in the former than the latter. According to Ishizaki et al.,[78] the clearance of omeprazole is slower in Korean and Chinese individuals compared to that in Caucasians. The higher proportion of heterozygous EMs in Asians (about twice as high as in Caucasians) is probably the main reason. However, there are also high interindividual/interethnic differences in the activity of CYP2C19 within homozygous EMs of this enzyme.

Variants identified in the regulatory (promoter) region of a given gene can contribute to the variable activity of an enzyme, as has been recently shown for the *CYP2C9* gene.[79] Of note, Tanzanian individuals have a lower capacity to metabolise (*S*)-mephenytoin, citalopram, diazepam, omeprazole and proguanil compared with Asians and Caucasians,[56,80] although the frequency of PMs was not more than 7.5%.[81] As can be clearly seen in table I, the variant alleles of *CYP2C19* identified so far involve the exonic and intronic regions of the *CYP2C19* gene. It is possible that yet unidentified variants in the promoter region of *CYP2C19* (for example in the Tanzanian population) contribute to this difference. The promoter region of the *CYP2C19* gene is less understood at this moment, but cloning of this region should facilitate further research to understand its significance in this respect. Nongenetic factors, including drugs that are inhibitors or inducers of CYP2C19 and disease states, may also contribute to the variability of CYP2C19 activity and the reason for high interindividual variability within homozygous EMs.

## 1.2 Inhibitor and Inducer Drugs

### *1.2.1 Inhibitors*

Successful quantification of individual CYP isoform activity *in vitro* and *in vivo* depends on the availability of isoform-specific substrate probe re-

actions and on the choice of isoform-specific chemical or immunological inhibitors. (*S*)-Mephenytoin remains the most reliable substrate reaction probe to measure the activity of CYP2C19 *in vivo* as well as *in vitro*, although omeprazole and proguanil are also used. Recent studies by us and by other authors have identified a number of CYP2C19 chemical inhibitors (table III). Most of these drugs lack selectivity towards CYP2C19 and cannot easily be used as tools to study the role of CYP2C19.

The only reasonable drug that appears selective and thus useful *in vitro* and *in vivo* as a diagnostic probe to study CYP2C19 inhibition is omeprazole. We have shown that omeprazole is a potent inhibitor of CYP2C19 [inhibition constant ($K_i$) 3 μmol/L).[94] *In vivo*, coadministration of omeprazole results in a significant increase in the area under the concentration-time curve (AUC) of diazepam in EMs of CYP2C19, with no effect on PMs.[117] The same has been reported with respect to inhibition of proguanil metabolism by omeprazole.[98] In both studies, there was no effect of omeprazole on pathways mediated by CYP3A.

Inhibition of CYP2C19 by omeprazole, a drug that is itself a substrate of this isoform, means that inhibition of CYP2C19 occurs in a gene dose dependent manner, in that maximum inhibition occurs in homozygous EMs > heterozygous EMs >> homozygous PMs. Thus, one ethnic group may be more sensitive to drug inhibition than another. Indeed, the degree of inhibition of (*S*)-mephenytoin and diazepam is dependent on ethnicity in EMs of CYP2C19, inhibition being much greater in European Caucasian than Chinese individuals.[96,97] The proportion of heterozygous EMs is about 2-fold greater in the Chinese than Caucasian population, and this over-representation of heterozygous genotypes of CYP2C19 among the Chinese EM individuals might have contributed to this ethnic-based difference in the inhibition of CYP2C19 by omeprazole. These data highlight the need to consider interethnic variability before extrapolating drug interaction data obtained in one ethnic group to another.

Although nonspecific, a number of other *in vitro* and/or *in vivo* inhibitors of CYP2C19 activity have been identified (table III) that may create a 'phenocopy' of the PM phenotype.

Because of the close homology of the CYP2C subfamilies, there has been no specific antibody against the CYP2C19 protein until recently. The recent discovery of a monoclonal antipeptide antibody against human CYP2C19[118] that selectively and potently inhibits the CYP2C19 activity of human hepatic microsomal fractions will be an important additional tool to indentify CYP2C19 activity *in vitro*.

#### 1.2.2 Inducers

Recent breakthroughs, such as the discovery of the expanded role for nuclear hormone receptors such as the constitutive androstane receptor (CAR), pregnane X receptor (PXR) and peroxisome proliferator-activated receptor (PPAR),[119] have greatly improved our understanding of the molecular mechanisms regulating the induction of drug-metabolising CYP enzymes. Currently, there are four main mechanisms of induction of drug-metabolising enzymes that are mediated by intracellular receptors. Those receptors are aryl hydrocarbon (Ah), PPAR, CAR (involved in induction by phenobarbital) and PXR [involved in induction by rifampicin (rifampin)].[119,120] Evidence from clinical drug interaction and phenotyping studies suggests that the *CYP 2C19* gene is inducible by at least two drugs *in vivo* in humans, rifampicin and artemisinin (table III), but the molecular mechanism of induction of this enzyme has not been clarified. This lack of study and present state of confusion about the regulation of this enzyme is largely due to the fact that the 5′regulatory region of *CYP2C19* is not fully understood.

Clinical studies conducted in the 1970s demonstrated that rifampicin induces the metabolism of hexobarbital, but the specific isoform involved was not clear at that time. Zilly et al.[113] reported about a 3-fold increase in the metabolic clearance of hexobarbital after healthy volunteers were pretreated with rifampicin (1200mg per day for 8 days). We now know that hexobarbital, particu-

larly the (*R*)-isomer, is a substrate of CYP2C19 *in vitro*[121] and *in vivo*.[114,121,122] Of note, induction of hexobarbital did not occur with corticosteroids.[123] It seems that elderly individuals are less sensitive than younger adults to induction of hexobarbital disposition by rifampicin, as rifampicin pretreatment produced a differential increase in (*R*)-hexobarbital metabolism in young (89-fold increase) and elderly (19-fold increase) individuals.[114]

Subsequent studies conducted using (*S*)-mephenytoin as probe drug by Zhou and coworkers as well as Wilkinson and coworkers have confirmed that rifampicin is an inducer of CYP2C19.[111,112] In the first study,[112] 13 healthy individuals were given rifampicin 600 mg/day for 22 days, which resulted in a 3- to 8-fold increase ($p < 0.01$) in the 0 to 8 hour urinary *R*/*S* ratio of mephenytoin, and a 40 to 180% increase in the 0 to 8 hour urinary excretion of the 4′-hydroxy metabolite, following oral administration of 100mg of racemic drug in individuals with the EM phenotype. In the second study,[111] they showed that the percentage increase in the 0 to 24 hour excretion of 4′-hydroxymephenytoin in CYP2C19 homozygous EMs was greater than that in heterozygous EMs (203.9 ± 42.5 *vs* 69.6 ± 4.1%). They concluded that the inducing effect of rifampicin on CYP2C19 is gene

**Table III.** *In vitro* and *in vivo* inhibition and induction of cytochrome P450 2C19

| Inhibitor/inducer | Substrate | Effect |
|---|---|---|
| **Inhibition** | | |
| Cimetidine | Proguanil[82] | *In vivo* |
| | Diazepam[83] | *In vivo* |
| Felbamate | (*S*)-Mephenytoin[84] | *In vitro* |
| Fluoxetine (norfluoxetine) | (*S*)-Mephenytoin[85-87] | *In vivo*, *in vitro* |
| Fluvoxamine | Omeprazole[88] | *In vitro* |
| | Proguanil[89] | *In vitro* |
| | (*S*)-Mephenytoin[85] | *In vitro*, *in vivo* |
| | Chlorguanide[90] | *In vivo* |
| Sertraline | (*S*)-Mephenytoin[86] | *In vitro* |
| Isoniazid | (*S*)-Mephenytoin, omeprazole[91] | *In vitro* |
| Ketoconazole | (*S*)-Mephenytoin[92,93] | *In vitro*, *in vivo* |
| Lansoprazole | (*S*)-Mephenytoin[94] | *In vitro*, *in vivo* |
| Omeprazole | Diazepam[95,96] | *In vivo*, *in vitro* |
| | (*S*)-Mephenytoin[94,97] | *In vitro*, *in vivo* |
| | Proguanil[98] | *In vitro*, *in vivo* |
| Esomeprazole | Diazepam, (*R*)-warfarin[99] | *In vivo* |
| Moclobemide | (*S*)-Mephenytoin[100] | *In vivo* |
| Oral contraceptives | Omeprazole and (*S*)-Mephenytoin[101] | *In vitro* |
| Loratadine | (*S*)-Mephenytoin[102] | *In vitro* |
| Tamoxifen | (*S*)-Mephenytoin[103] | *In vitro* |
| Ticlopidine | Omeprazole[104,105] | *In vivo* |
| | (*S*)-Mephenytoin[106,107] | *In vitro* |
| Topiramide | (*S*)-Mephenytoin[108] | *In vitro* |
| Tranylcypromine | (*S*)-Mephenytoin[109] | *In vitro* |
| Papaverine | (*S*)-Mephenytoin[109] | *In vitro* |
| Zonisamide | (*S*)-Mephenytoin[110] | *In vitro* |
| **Induction** | | |
| Rifampicin (rifampin) | (*S*)-Mephenytoin[111,112] | *In vivo* |
| | Hexobarbital[113,114] | *In vivo* |
| Artemisinin | Omeprazole[115,116] | *In vivo* |

dose dependent. Other authors have recently reported similar findings.[124]

Recent evidence using omeprazole as a probe suggests that artemisinin, an effective antimalarial drug, is a potent inducer of CYP2C19. Svensson et al.[116] studied the effect of artemisinin on omeprazole metabolic clearance. Healthy male Vietnamese volunteers received oral artemisinin 250mg twice daily for 7 days and the pharmacokinetics of omeprazole (20mg single oral dose) was evaluated on days –7, 1, 7 and 14. They found that the AUC of omeprazole was decreased by 35% (confidence interval 25 to 46%) and the AUC ratio of 4′-hydroxy-omeprazole/omeprazole increased 2.2-fold on day 7 compared with day 1. In this study, artemisinin had no effect on CYP3A activity as measured by omeprazole sulfone formation and 6β-hydroxycortisol/cortisol ratio.[116] A subsequent study by Mihara et al.[115] showed that 7 days of artemisinin administration significantly decreased the AUC of both omeprazole enantiomers and increased the AUC ratio of (*R*)-5-hydroxy-omeprazole to (*R*)-omeprazole. Both studies[115,116] suggested that artemisinin is an inducer of CYP-2C19-mediated 5′-hydroxylation of the (*R*)-enantiomer of omeprazole, while an unidentified enzyme other than CYP2C19 and CYP3A might have been involved in (*S*)-omeprazl metabolism.

Phenytoin has been suggested to induce its own metabolism in humans,[125] but it seems difficult to conclude whether this induction is due to an effect on CYP2C9 or CYP2C19. The formation of the (*S*)-enantiomer of 4′-hydroxy-phenytoin from phenytoin is catalysed mainly by CYP2C9 and that of the (*R*)-enantiomer is catalysed mainly by CYP2C19.[126,127] The 4′-hydroxylation of phenytoin is highly stereoselective towards formation of the (*S*)-enantiomer, which suggest that this pathway is the major determinant of phenytoin disposition.[126,127] Unless the formation of the specific phenytoin metabolite enantiomers is measured, it is difficult to attribute autoinduction of phenytoin to induction of CYP2C19. Clearly, more studies are needed to determine whether phenytoin is an inducer of CYP2C19.

It is clear that CYP2C19 can be induced by rifampicin, but the mechanism of this effect remains unclear. Artemisinin induces CYP2C19 without having effect on CYP3A. Carbamazepine, a known inducer of CYP3A, has been shown to increase the formation of CYP3A-mediated omeprazole sulfone, with no effect on the activity of CYP2C19 *in vivo*.[128] Phenobarbital has been shown to have no effect on the 4′-hydroxylation of (*S*)-mephenytoin in humans.[129]

As *in vitro* studies in human hepatocytes or hepatoma cell lines, and mechanistic human *in vivo* studies on CYP2C19 induction are sparse, a great number of studies of drug effect on CYP2C19 remain to be performed. In order to facilitate understanding of the molecular mechanisms regulating the induction of CYP2C19 by xenobiotics and endogenous substances, it was necessary to clone and sequence the 5′-regulatory region of *CYP2C19* that regulates the activity of the enzyme. We have recently reported the sequence of 1.8kb of this region,[130] but further mechanistic studies of the upstream region and identification of xenobiotic response elements is important to fully understand the induction of CYP2C19.

### 1.3 Disease, Age and Gender

The activity of CYP2C19 has been documented to be moderately reduced in liver disease[131-134] and has therefore been proposed as an index of hepatic function,[135] in cancer patients[136] and in patients with eosinophilia-myalgia syndrome.[137] There is evidence that in old age the activity of this enzyme may be reduced.[138] The ability of rifampicin to induce CYP2C19-mediated (*R*)-hexobarbital clearance is diminished in elderly compared with young healthy volunteers.[114]

The effect of gender on the activity of CYP-2C19 is controversial. Studies in healthy volunteers report no effect of gender,[101,139] or higher activity in females than in males,[140] or higher activity in males than in females.[55] These data suggest that gender is not an important factor in modulating the activity of CYP2C19.

## 2. Clinically Relevant Substrates of CYP2C19

Rapid progress in the field of CYP enzymology in recent years has allowed researchers to identify the specific CYP isoforms involved in the enzymatic reactions that occur during drug metabolism. The participation of CYP2C19 in the metabolism of a drug can therefore be tested *in vitro* using different approaches, including use of correlation analysis between CYP2C19 activity (protein content) in microsomes from a panel of human livers and rate of metabolism of a specific substrate drug, specific chemical and immunological inhibitors, and kinetic analysis in human liver preparations and recombinant human CYP2C19. Molecular modelling of CYP2C19 has been reported based on an alignment with a bacterial form of the enzyme, CYP102, using omeprazole and other substrates.[141] Further characterisation of the three-dimensional structure of human CYP2C19 may in the future allow predicting substrates of the enzyme and what metabolites may be expected.

*In vivo* human pharmacokinetics of the substrate in question in CYP2C19 genotyped and/or phenotyped individuals have remained instrumental in defining the role of CYP2C19 in drug metabolism. The ability of drugs to inhibit or induce CYP2C19 can be quantified *in vivo* in humans by comparing the formation of a specific metabolite of an appropriate probe drug in urine or plasma in control and drug-treated groups.

Using appropriate *in vitro* and *in vivo* probes, CYP2C19 has been shown to metabolise not only (*S*)-mephenytoin, but also an increasing number of clinically important drugs. Although most of its documented functions involve detoxification of drugs, this enzyme is also able to convert drugs to pharmacologically active molecules (e.g. diazepam to desmethyldiazepam,[142,143] proguanil to cycloproguanil[144] and nelfinavir to its major circulating active metabolite, M8).[134,145] CYP2C19 is involved in both primary and secondary metabolism (e.g. omeprazole sulfone or desmethyldiazepam). At least *in vitro*, this isoform is involved in the biotransformation of endogenous[146] and environmental substances.[147] The CYP2C19 substrates acted upon may be neutral (e.g. diazepam, pKa 3.3), weak bases (e.g. proguanil, pKa 10.4, and propranolol) or weak acids (e.g. mephenytoin).[141] The structural dissimilarity between the substrates suggests that the three-dimensional requirement for binding to this enzyme is not rigid.

The drugs metabolised, and the respective metabolic pathways catalysed, by CYP2C19 are summarised in table IV. The substrates may be divided into three categories based on the contribution of CYP2C19 to the overall oral clearance of the drugs: ≥80% [e.g. omeprazole, lansoprazole, pantoprazole, (*S*)-mephenytoin, (*R*)-mephobarbital, (*R*)-hexobarbital and carisoprodol], 30 to 65% (e.g. proguanil, imipramine, clomipramine, moclobemide, diazepam, flunitrazepam, citalopram, sertraline and fluoxetine) and <30% (e.g. phenytoin, propranolol).[19,148-150]

### 2.1 Proton Pump Inhibitors

The $H^+/K^+$-ATPase (proton pump) inhibitors (PPIs) have dramatically influenced the management of acid-peptic disorders in recent years. These drugs are useful for the relief of symptoms and healing of gastro-oesophageal reflux disease (GORD), gastric and duodenal ulcer disease, eradication of *H. pylori* infection, prevention and treatment of nonsteroidal anti-inflammatory drug (NSAID)-associated damage, management of hypersecretory states such as Zollinger-Ellison syndrome, and care of patients with non-variceal upper gastrointestinal bleeding or non-ulcer dyspepsia.[191] All the PPIs are prodrugs and have similar mechanisms of action. After oral administration, they are absorbed into the systemic circulation, enter the gastric parietal cells from the plasma and are rearranged nonenzymatically to active sulfenamide derivatives that bind covalently (irreversibly) to a sulfhydryl group of $H^+/K^+$-ATPase in the acidic conditions of the parietal cell canaliculus. The PPIs cause prolonged inhibition of the proton pump that exceeds their relatively short plasma elimination half-lives.[192] They all are effective for the acute and chronic treatment of

GORD and demonstrate similar short- and long-term safety profiles.[193] It seems that selection among the drugs is dependent on acquisition cost, there being little evidence that drug interaction profiles or therapeutic efficacy are significantly different between them.[193]

**Table IV.** Drugs and other agents whose metabolic pathway cosegregates with the activity of cytochrome P450 2C19 *in vitro* and/or *in vivo*

| |
|---|
| **Proton pump inhibitors** |
| Omeprazole 5-hydroxylation[151,152] |
| Lansoprazole 5-hydroxylation[153,154] |
| Pantoprazole *O*-demethylation[155] |
| Rabeprazole *N*-demethylation[156,157] |
| **Anticonvulsants, hypnosedatives, muscle relaxants** |
| Phenytoin 3′- and 4′-hydroxylation[127,158] |
| (*S*)-Mephenytoin and nirvanol 4′-hydroxylation[9,12,159] |
| Methylphenytoin 4′-hydroxylation[160] |
| Diazepam *N*-demethylation (activation)[142,161,162] |
| Desmethyldiazepam hydroxylation[142] |
| Flunitrazepam *N*-demethylation[148,163] |
| Phenobarbital *p*-hydroxylation[164] |
| (*R*)-Hexobarbital 3′-hydroxylation[121,165] |
| (*R*)-Mephobarbital 4-hydroxylation[166,167] |
| Carisoprodol *N*-demethylation[168,169] |
| **Anti-infectives** |
| Proguanil cyclisation (activation)[50,170-173] |
| Chlorproguanil cyclisation (activation)[173] |
| Nelfinavir hydroxylation (activation)[134] |
| **Antidepressants** |
| Citalopram *N*-demethylation[174] |
| Fluoxetine *N*-demethylation[149] |
| Sertraline *N*-demethylation[150] |
| Venlafaxine *O*-demethylation (activation)[175] |
| Imipramine *N*-demethylation[176-178] |
| Clomipramine *N*-demethylation[179] |
| Trimipramine[180] |
| Amitriptyline *N*-demethylation[181] |
| Nortriptyline demethylation[182] |
| Moclobemide *C*-hydroxylation[100] |
| **Others (mainly *in vitro* evidence)** |
| Thioridazine[183] |
| Propranolol side-chain oxidation[184] |
| Tolbutamide 4-hydroxylation[185] |
| (*R*)-Warfarin 8-hydroxylation[186] |
| Progesterone 21-hydroxylation[146,187] |
| Testosterone oxidation at 17-position[146,187] |
| Desogestrel 3α-hydroxylation (activation)[188] |
| Cyclophosphamide 4-hydroxylation (active)[189] |
| Ifosfamide 4-hydroxylation (active)[190] |
| Methoxychlor *O*-demethylation (activation)[147] |

#### *2.1.1 Effect of CYP2C19 Genetic Polymorphism on Metabolism, Pharmacokinetics and Response*

Four PPIs are now available in the US: omeprazole, lansoprazole, pantoprazole and rabeprazole. The (*S*)-enantiomer of omeprazole, esomeprazole, has been also been approved recently. These drugs have similar chemical structure, a pyridinyl-sulfinylbenzimidazole backbone, and undergo extensive primary metabolism in the liver at the sites indicated in figure 1. Omeprazole is hydroxylated at the 5-methyl group, primarily by CYP2C19, and undergoes sulfoxidation to omeprazole sulfone by CYP3A.[194,195] Lansoprazole undergoes 5-hydroxylation and sulfoxidation by CYP2C19 and CYP3A, respectively[154,196] but, unlike omeprazole, lansoprazole has no 5-methyl group and the hydroxylation takes place on the benzimidazole ring (figure 1). Other minor routes of omeprazole metabolism include CYP3A-catalysed 3-hydroxylation and CYP2C19-mediated 5-*O*-demethylation.[194] The hydroxylated and sulfone metabolites of omeprazole are then further metabolised to the hydroxysulfone derivative via CYP3A and CYP2C19, respectively.[197] Thus both CYP2C19 and CYP3A are sequentially – but alternatively – involved in the metabolism of omeprazole and most probably also of lansoprazole.

The main metabolic pathway of pantoprazole is demethylation at the 4-position of the pyridine ring by CYP2C19, and subsequent conjugation with sulfate by sulfotransferase.[155,198] Part of pantoprazole is converted to pantoprazole sulfone by CYP3A.[155]

Rabeprazole is converted primarily to rabeprazole thioether nonenzymatically, but some is oxidised to demethylated rabeprazole and rabeprazole sulfone by CYP2C19 and CYP3A, respectively.[157,198]

The routes and the enzymes involved in esomeprazole metabolism are essentially similar to those described for omeprazole, except that the rate of 5′-hydroxylation is slow for esomeprazole

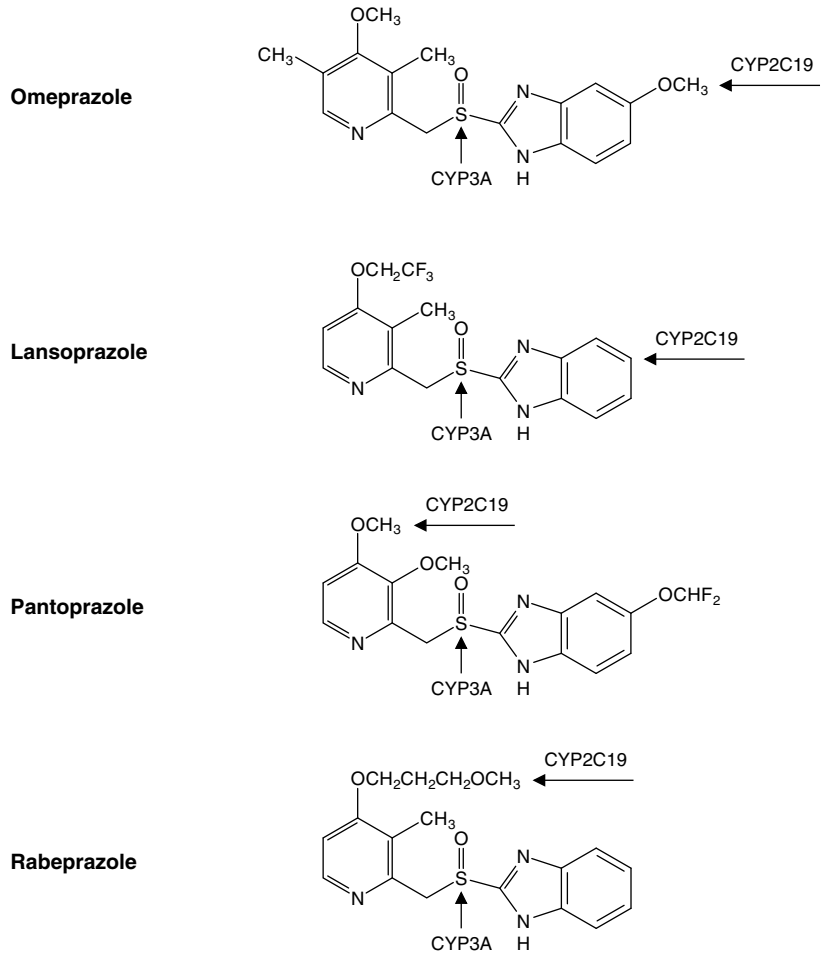


**Fig. 1.** Chemical structures of proton pump inhibitors. Arrows indicate major sites of cytochrome P450 (CYP)-mediated sulfoxidation by CYP3A and oxidation by CYP2C19.

compared to the racemic mixture.[199] Indeed, studies have shown that the metabolism of these drugs by CYP2C19 is stereoselective.[195,200-202] All PPIs have asymmetric sulfur atoms. Frequently, enantiomers differ in their pharmacokinetics, pharmacodynamics, drug interactions and adverse effects. Although the clinical relevance of this to the effects of these drugs is not yet fully established, it has led to the development of esomeprazole. Together, these *in vitro* data indicate major roles for CYP2C19 and CYP3A in the primary and secondary metabolism of PPIs.

The *in vitro* findings are supported by data obtained from studies conducted in PMs and EMs of CYP2C19. Early clinical studies indicated a considerable interindividual variation in omeprazole elimination.[203] Later, this was shown to be due to differences among individuals in the activity of CYP2C19. In PMs of CYP2C19, the plasma concentration or AUC of omeprazole, lansoprazole or

pantoprazole is approximately 5-fold higher in PMs than in EMs of CYP2C19.[204] It is estimated that ~80% of doses of these drugs is cleared by CYP2C19 in EMs.[204] Slightly lower plasma concentrations and AUC of esomeprazole are observed compared with omeprazole in PMs of CYP2C19, but the effect of CYP2C19 genetic polymorphism on esomeprazole is consistent with a major role of CYP2C19 in the elimination of this drug.[199] The clearance of rabeprazole *in vivo* appears to be less influenced by CYP2C19 when compared with other PPIs. For example, Yasuda et al.[156] have shown that the mean values for AUC of omeprazole were 6.3- to 4.4-fold greater, whereas those of rabeprazole were 1.8- and 1.9-fold greater, in PMs than in EMs of CYP2C19 after the first and last doses, respectively.

All in all, the CYP2C19 route is quantitatively an important determinant of the elimination of omeprazole, lansoprazole, pantoprazole and esomeprazole. The contribution of CYP3A to the elimination of PPIs is limited in EMs of CYP2C19, but it is the main route of elimination in PMs or if the metabolic activity of CYP2C19 is significantly diminished by a drug interaction.[205]

The PPIs are relatively well tolerated at the standard doses used, and even the 5-fold increase in the AUC of PPIs in PMs appears to result in negligible adverse effects. However, recent evidence strongly suggests that the wide interindividual variation in the pharmacokinetics of PPIs is reflected in a wide range of acid suppression by standard doses of PPIs. Individuals with slow clearance and higher drug concentrations of PPIs do experience superior acid suppression, which might confer improved therapeutic effectiveness in some settings. Chang et al.[206] have clearly demonstrated that omeprazole therapy increases the AUC of gastrin in plasma more in PMs than in heterozygous EMs or homozygous EMs, and that these differences were correlated with the AUC of omeprazole in plasma. Furuta et al.[207] tested whether the effect of omeprazole on intragastric pH depends on CYP2C19 genotype status in 16 healthy volunteers. They found that after a single 20mg dose of omeprazole, significant differences in mean intragastric pH values and plasma concentrations of gastrin, omeprazole and its metabolites were observed among the EMs and PMs of CYP2C19, whereas no significant differences in these parameters were observed during placebo administration. Sagar et al.[208] recently demonstrated that long-term administration of omeprazole not only alters intragastric pH and plasma gastrin levels, but also affects several other pharmacodynamic parameters, including pepsinogen I, plasma chromogranin A and oxyntic mucosa, in a manner consistent with genetic ability to metabolise omeprazole. They suggested that omeprazole might alter gastric mucosal morphology in a concentration-dependent manner.

Recent studies conducted in EMs and PMs of CYP2C19 strongly suggest that genotyping of CYP2C19 might be an important tool in guiding therapy with the PPIs. The first such report came from Furuta et al.,[209] who showed that treatment with omeprazole 20 mg/day plus amoxicillin brought about eradication of *H. pylori* infection in 28.6, 60 and 100% of homozygous EMs, heterozygous EMs and PMs of CYP2C19, respectively, and that this cure rate was parallel with the healing rates for both duodenal and gastric ulcers in the respective three groups (see figure 2). Other authors later confirmed these findings. Aoyama et al.[210] studied 86 patients with culture-confirmed *H. pylori*-positive gastritis or peptic ulcers who completed dual or triple treatment containing omeprazole, and showed that PMs had higher cure rates than EMs in both dual or triple therapy regimens. Tanigawara et al.[211] compared the *H. pylori* eradication rate in 180 patients genotyped for CYP2C19 who were on no omeprazole or with omeprazole included in a dual or triple therapy. They found that all PMs had complete eradication after both dual and triple therapy, whereas EMs had 50 and 86% cure rates after dual and triple therapy, respectively, suggesting that dual therapy containing omeprazole and one antibacterial is adequate in PMs. In one clinical case report, Furuta et al.[212] noted that a patient who was a documented EM of

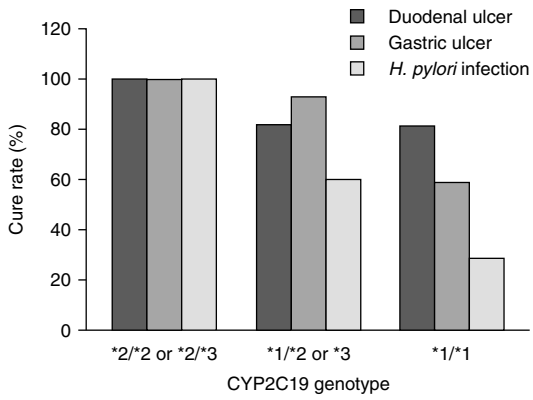


**Fig. 2.** Cure rates of *Helicobacter pylori* infection and healing rates of gastric and duodenal ulcers in patients treated with omeprazole 20 mg/day for 6 to 8 weeks and amoxicillin 200 mg/day for 2 weeks in three cytochrome P450 (CYP) 2C19 genotype groups. A gene dose effect was observed for the cure and healing rates (poor metabolisers > heterozygotes > wild type for CYP2C19).[209]

CYP2C19 was refractory to PPI-based triple therapy, but responded to dual therapy containing high dosage omeprazole (120 mg/day) and amoxicillin.

The link between efficacy and genetic polymorphism of CYP2C19 has been studied primarily using omeprazole, but the case may be the same with lansoprazole[213] and probably pantoprazole. However, compared with other PPIs, the primary metabolism of rabeprazole is less dependent on CYP2C19. The effect of genetic polymorphism of CYP2C19 on rabeprazole efficacy is not clear. Recently, Furuta et al.[214] studied 97 patients with gastritis and *H. pylori* infection who completed dual therapy with rabeprazole 10mg twice daily and amoxicillin 500mg three times daily for 2 weeks. They found higher cure rates for *H. pylori* infections in PMs of CYP2C19 (93.8%) and in heterozygous EMs (91.7%) compared with homozygous EMs (60.6%). It was suggested by the authors that rabeprazole thioether, which is produced by nonenzymatic reduction and whose further metabolism may be catalysed by CYP2C19, might contribute to the effect of rabeprazole. Conversely, other authors have shown that the efficacy of rabeprazole as acid suppressant[213] and against *H. pylori* in triple therapy[215] does not depend on CYP2C19 genotype.

#### *2.1.2 Interactions with the CYP System*

Since CYP-mediated metabolic drug interactions are often dependent on substrate and inhibitor/inducer concentrations, it is possible that the genetic polymorphism of CYP2C19 contributes to pharmacokinetic interactions of the PPIs with other drugs. Concomitant administration of other drugs that are inhibitors or inducers (table III) of CYP2C19 would be expected to influence the pharmacokinetics of PPIs and other CYP2C19 substrates in a gene dose dependent manner, i.e. the degree of interaction is greatest in individuals who are homozygous EMs, less in heterozygous EMs and least in PMs of CYP2C19. Drugs such as ticlopidine[105] and oral contraceptives[101] have been shown to inhibit 5′-hydroxylation of omeprazole and thereby significantly slow its elimination in normal volunteers. *In vitro*, fluvoxamine inhibits the 5′-hydroxylation of omeprazole.[88] Clearly, strong inhibition of PPI metabolism in EMs of CYP2C19 can be achieved by concomitant administration of other drugs, but whether inhibition of CYP2C19 may influence therapeutic outcome needs to be assessed.

In PMs of CYP2C19, CYP3A-mediated metabolism of the PPIs appears to be dominant and potent inhibition of this isoform significantly slows the elimination of PPIs. For example, Furuta et al.[216] have shown that the mean $AUC_{24}$ of omeprazole in homozygous EMs, heterozygous EMs and PMs was significantly increased by clarithromycin from 384 to 813, from 1002 to 2110, and from 5590 to 13099 μg • h/L, respectively. Zhou et al.[205] have reported a similar effect of clarithromycin on omeprazole elimination. According to Bottiger et al.,[217] oral ketoconazole 100 to 200 mg/day markedly inhibited the formation of omeprazole sulfone in both EMs and PMs and led to a doubling of omeprazole plasma concentrations. These data show that inhibition of CYP3A-mediated alternative pathways in PMs, or dual inhibition of CYP3A and CYP2C19 in EMs

(for example by ketoconazole, clarithromycin + omeprazole or clarithromycin + ticlopidine), could significantly alter the pharmacokinetics and the acid-suppressing effect of the PPIs. Of note, inhibition of CYP3A in PMs of CYP2C19 (for example by ketoconazole) doubles the AUC of omeprazole and results in a net 10-fold higher AUC of this drug in PMs compared with EMs who did not take an inhibitor of CYP3A.[217] It is conceivable that patients whose CYP2C19 and CYP3A are inhibited respond better to PPI therapy for *H. pylori* infection.

Induction of the metabolism of PPIs is less well investigated. It is possible that concomitant administration of CYP2C19 inducers (table III) reduces the efficacy of PPIs in EMs by enhancing their clearance, but there is no comparative clinical study to test this hypothesis. Artemisinin has been shown to increase the rate of 5′-hydroxyomeprazole formation in humans.[115,116] When the activity of CYP2C19 is diminished (by genetic or environmental factors), the CYP3A-mediated pathway is an alternative elimination route for the PPIs. A number of drugs, and herbal medications such as St John's Wort, that enhance the activity of this isoform[218,219] are likely to induce the metabolism of PPIs and decrease the effective concentration in plasma. Carbamazepine at 400 to 600 mg/day has been shown to markedly induce the formation of omeprazole sulfone in patients.[128] Such induction is particularly marked in PMs of CYP2C19, where CYP3A is the major metabolic route. Because the inducers of CYP2C19 so far identified, such as rifampicin, are nonselective, and since the metabolism of the PPIs is mediated by both CYP2C19 and CYP3A, the precise contribution of CYP2C19 induction to PPI metabolism is difficult to establish, especially in heterozygous EMs. Given that the efficacy of these drugs depends in part on CYP2C19 genotype, and that the dosage range of these drugs varies under different conditions (for example, the dosage of omeprazole ranges from 20 to 120 mg/day), coadministration of rifampicin and other inducers with omeprazole, lansoprazole and pantoprazole in homozygous EMs might be a reason for failure of therapy, especially when dosages at the lower end of the recommended range are used, but controlled clinical studies are required to support this suggestion.

Certain PPIs may alter the pharmacokinetics of coadministered drugs by interacting with the CYP system. The most widely studied interaction in this respect is the effect of omeprazole, but not lansoprazole,[220] on the metabolism of diazepam.[17,83,95,96,117,221,222] *In vitro*, we have shown that omeprazole and lansoprazole are potent inhibitors of CYP2C19, with a $K_i$ of less than 4 μmol/L.[94] Omeprazole has been shown to reduce the clearance of other CYP2C19 substrates, including proguanil,[82] phenytoin[82,222,223] and cilostazol.[224] The sulfone metabolite of omeprazole is a substrate of CYP2C19 and contributes to this inhibition.[194,197,221] Of note, omeprazole interactions with diazepam and proguanil occur in a gene dose dependent manner, with high interaction in EMs and no interaction in PMs of CYP2C19, as this enzyme is deficient in this group of individuals. Esomeprazole has similar drug interaction profiles as omeprazole in that it competitively interferes with CYP2C19 to slow the elimination of phenytoin, diazepam, (*R*)-warfarin and cisapride.[99] There is evidence that omeprazole and esomeprazole may inhibit their own metabolism *in vivo*.[199,225]

It is conceivable that the up to 5-fold increases in plasma concentrations or AUCs of the parent drugs and the corresponding sulfone metabolite of omeprazole in PMs relative to EMs of CYP2C19 may enhance the degree of drug interaction of the PPIs with other drugs whose metabolic pathways are independent of CYP2C19. Recently, multiple doses of omeprazole have been shown to increase the peak concentration ($C_{max}$), AUC and elimination half-life of carbamazepine,[226] a drug whose metabolic pathways are catalysed by CYP2C8 and CYP3A. Although there is no evidence that the PPIs inhibit major drug-metabolising CYP isoforms other than CYP2C19 in a significant way,[94,199] the possibility that the PPIs may inter-

act with less characterised isoforms (e.g. CYP2C8 and CYP2B6) cannot be excluded.

There is *in vitro* evidence that omeprazole and other PPIs induce the activities of CYP1A1 and 1A2 in a dose-dependent manner.[227] The first evidence of CYP1A2 induction by omeprazole in healthy volunteers was based on the study of Rost et al.,[228] in which enhanced metabolism of caffeine, a substrate probe of CYP1A2,[229] was reported. This effect was greater in individuals who were PMs of CYP2C19. Indeed, subsequent studies by Rost et al.[225,230] and Nousbaum et al.[231] have further confirmed that omeprazole enhances the CYP1A2-mediated metabolism of caffeine. Although clinical studies have been conducted to demonstrate that other PPIs such as pantoprazole[232] might be less prone than omeprazole to drug interactions resulting from induction of CYP1A2, several authors have questioned the clinical relevance of induction of CYP1A2 by the PPIs. Andersson et al.[204] have studied the induction of CYP1A2 by omeprazole 20mg, lansoprazole 30mg or pantoprazole 40mg after single oral doses and multiple doses over 7 days in healthy male EMs and PMs of CYP2C19. They found that none of these drugs induced caffeine metabolism in EMs or PMs of CYP2C19 at day 1 or day 7. Other studies,[233-235] including our own study in Caucasians and Koreans,[236] have shown that omeprazole, lansoprazole and pantoprazole do not affect the elimination of theophylline, a drug primarily cleared by CYP1A2, irrespective of whether the individuals are PMs or EMs of CYP2C19. Together, the data presented so far do not support the idea that induction of CYP1A2 is important in terms of clinically significant drug interactions, and it is unlikely that choice among the different PPIs would be based on their ability to interact with other drugs via induction of CYP1A2.

#### *2.1.3 Plasma Levels of Cyanocobalamin*

Reduced serum vitamin $B_{12}$ (cyanocobalamin) concentrations have been documented occasionally during long-term treatment with PPIs in selected groups of patients, particularly in patients being treated for Zollinger-Ellison syndrome who have sustained drug-induced achlorhydria.[237] Recent work by Sagar et al.[238] has provided direct evidence that this effect on vitamin $B_{12}$ absorption can be influenced by CYP2C19 (see figure 3). They studied the effect of either a single 20mg oral dose of omeprazole (n = 111) or long-term daily treatment with the same dose for more than a year (n = 68) in patients phenotyped and genotyped for CYP2C19 who had peptic ulcer disease or GORD with oesophagitis. Long-term treatment with omeprazole significantly reduced vitamin $B_{12}$ plasma concentrations in heterozygous EMs relative to homozygous EMs (305 ± 98 pmol/L in homozygotes versus 246 ± 71 pmol/L in heterozygotes, $p < 0.01$) and when compared with single dose treatment in heterozygous EMs (350 ± 82 pmol/L, $p < 0.0001$). They studied only one homozygous PM individual, but it is important to note that his serum

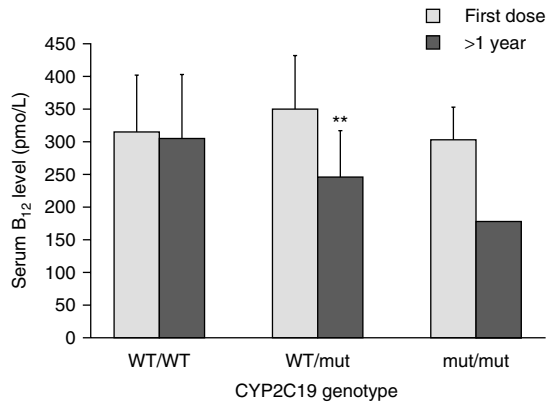


**Fig. 3.** Effect of omeprazole treatment on serum vitamin $B_{12}$ levels in patients genotyped for cytochrome P450 (CYP) 2C19. Values are means ± SD. Vitamin $B_{12}$ levels were determined after a single 20mg oral dose in *1/*1 (WT; n = 85), *1/*2 or *3 (WT/mut; n = 23) and *2/*2 (mut/mut; n = 3) and after long-term administration (oral omeprazole 20 mg/day for >1 year) in *1/*1 (n = 49), *1/*2 or *3 (n = 19) and *2/*2 (n = 1). ** indicates that chronic treatment with omeprazole for >1 year diminished vitamin $B_{12}$ serum levels significantly in the *1/*2 or *3 (heterozygous) genotyped patients ($p < 0.01$ versus *1/*1 genotyped patients; $p < 0.0001$ versus single dose of omeprazole in *1/*2 or *3 genotyped patients). Although only one patient with *2/*2 genotype completed the long-term treatment protocol, it is important to note that his $B_{12}$ serum level decreased from 360 (single dose) to 178 (>1 year treatment) pmol/L.[238]

vitamin $B_{12}$ level decreased from 360 pmol/L after a single dose to 178 pmol/L after over 1 year of treatment with omeprazole.

Although other authors have reported reduced vitamin $B_{12}$ levels during long-term omeprazole therapy (reviewed by Howden[237]), no studies have categorised patients according to their CYP2C19 metabolic status. Whether the reduction of vitamin $B_{12}$ could have clinical consequences in terms of development of megaloblastic anaemia or neuronal damage remains unclear. In a recent review, Howden[237] suggested that the use of PPIs does not in general promote the development of such anaemia. A single case of cobalamin deficiency with megaloblastic anaemia after long-term omeprazole treatment has been reported,[239] but the CYP2C19 genotype of this individual was not described. Currently, there are no clinical data to support that standard doses of PPIs promote the development of degenerative neuronal disease and pernicious anaemia, or whether PMs of CYP2C19 are at greater risk for such adverse effects.

#### 2.1.4 Omeprazole Therapy and Costs of Pharmacogenetic Testing

Data indicating that CYP2C19 genotype can alter the efficacy of omeprazole treatment have been available since 1998.[209] We have used these data to estimate the costs and benefits of CYP2C19 genotyping in the context of treatment of *H. pylori* infection with omeprazole and amoxicillin.

Conventional methods of genotyping involving restriction fragment analysis using agarose gel electrophoresis appear robust and rapid in our hands,[34,70] and we estimate the cost per allele analysed to be approximately $US10 at most. The cost of testing for CYP2D6 has been estimated by Chen et al.[240] as $US84 for six alleles, i.e. $US14 per allele. Rapidly evolving technologies involving rapid throughput[241] and chip technologies[242] may significantly lower this estimate, and it should be considered a conservative one at present. The cost of testing for the three principal *CYP2C19* alleles (*CYP2C19*1*, *CYP2C19*2* and *CYP2C19*3*) would therefore be $US30 per patient.

If the cost of treatment only with omeprazole is considered (taking the cost of amoxicillin as negligible as is the case in many countries), and if we use the average wholesale price in the US as of February 2001 ($US124.17 for 30 × 20mg capsules[243]), then the cost of therapy for 1 month would be $US124.17. We calculate that PMs would be treated for only 1 month, and that heterozygotes could be treated for only 2 months, as seems possible from the data of Furuta et al.[209]

From these assumptions, calculation of the overall cost of treatment can be made and the cost of treating nongenotyped and pregenotyped groups can be compared, as indicated in table V. Using these conservative assumptions, it would appear that genotyping for CYP2C19 could save approximately $US5000 for every 100 individuals of Asian ethnicity tested. This saving would increase if the cost of physician office visits were included or if the incidence of PMs were greater than 15% in the population under study. This of course does not include the cost to the patient of the longer period of adverse effects that might reasonably have been avoided.

Generally, the risks of pharmacogenetic testing are minimal. Procedurally, adequate DNA for genetic testing can be obtained from a single 1ml venous blood draw or from a buccal swab, with minimal risk. The estimates indicate that pregenotyping before the start of PPIs (omeprazole, pantoprazole and lansoprazole) may be cost effective. Genotyping for CYP2C19 seems to be a clinically useful tool for optimal treatment selection of PPI-based therapy for *H. pylori* eradication or reflux disease. This may enable physicians to determine the duration of treatment and dosage regimen of the PPIs and to determine the appropriateness of dual or triple therapy. About 65 to 70% of Asians are heterozygous EMs or PMs of CYP2C19, whereas this figure is lower (20 to 25%) in Caucasians (table II). Genotyping may save money and time, at least in populations with a relatively high incidence of PMs of CYP2C19.

Because the current conventional triple therapy of *H. pylori* infection has some drawbacks (e.g.

**Table V.** Cost-effectiveness analysis of genetic testing for *CYP2C19* alleles (*CYP2C19*1*, *CYP2C19*2* and *CYP2C19*3*) in Orientals and Caucasians. All costs are in US$ at 2001 values

| Component | Calculation | Total |
|---|---|---|
| Cost of omeprazole (20mg tablet once daily) for 1 month | | $US124[243] |
| Cost of CYP2C19 genotyping for three alleles per patient | | $US30[a] |
| **For 100 Asians** | | |
| 15 PMs stop after 1 month | 15 × $US124 | $US1860 |
| 40 heterozygous EMs stop after 2 months | 40 × 2 × $US124 | $US9920 |
| 45 homozygous EMs stop after 3 months | 45 × 3 × $US124 | $US16 740 |
| Total cost of therapy | | $US28 520 |
| Cost of genetic testing | 100 × $US30 | $US3000 |
| Total cost of genetic testing and therapy | | $US31 520 |
| Total cost without genetic testing | 100 × 3 × $US124 | $US37 200 |
| Saving from genetic testing | | $US5680 (or $US5.68/patient) |
| **For 100 Caucasians** | | |
| 3 PMs stop after 1 month | 3 × $US124 | $US372 |
| 18 heterozygous EMs stop after 2 months | 18 × 2 × $US124 | $US4464 |
| 79 homozygous EMs stop after 3 months | 79 × 3 × $US124 | $US29 388 |
| Total cost of therapy | | $US34 224 |
| Cost of genetic testing | 100 × $US30 | $US3000 |
| Total cost of genetic testing and therapy | | $US37 224 |
| Total cost without genetic testing | | $US37 200 |
| Saving from genetic testing | | $US4 (or $US0.04/patient) |

a The cost of genotyping test for *CYP2D6* alleles estimated by Chen et al.[240] was used as a basis for estimating the cost for genotyping *CYP2C19* alleles.

**CYP** = cytochrome P450; **EM** = extensive metaboliser; **PM** = poor metaboliser.

bacterial resistance to clarithromycin and metronidazole, adverse drug interactions 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, in that CYP2C19 genotyping may allow determination of an effective dosage regimen, including whether dual or triple therapy should be used. In years to come, it seems very possible that patients will be screened routinely for CYP2C19 genotype before PPIs are prescribed.

### 2.2 Anticonvulsants and Hypnosedatives

Several old or new anticonvulsants and hypnosedative drugs of diverse chemical structure are metabolised, at least partly, by CYP2C19 and other CYP2C isoforms. Many of them have a narrow therapeutic range. Besides the direct effect of genetic polymorphism on the elimination of the parent drug, which may be responsible for the intended therapeutic effect, the association between metabolites and toxicity remains largely unexplored.

The role of CYP2C19 in the metabolism of (*S*)-mephenytoin and its active metabolite nirvanol, and the role of genetic polymorphism of this enzyme in the safety of these drugs, has been well studied. Sedation has been observed after administration of mephenytoin to PMs of CYP2C19,[8] which prompted researchers to reduce the dose or use alternative substrate probes. This drug is now generally of little therapeutic importance, except that it is a widely and successfully used *in vitro* and *in vivo* probe of CYP2C19. Schellens et al.[160] have shown that the formation of 4-hydroxymethylphenytoin from methylphenytoin cosegregates with the 4-hydroxylation of (*S*)-mephenytoin, but this preparation is rarely used.

In the following sections we describe in detail the relationship between CYP2C19 genetic polymorphism and the elimination, therapeutic efficacy and adverse reactions of frequently prescribed anticonvulsant and hypnosedative drugs, with emphasis on diazepam, flunitrazepam, phenytoin, carisoprodol and phenobarbital.

#### 2.2.1 Benzodiazepines (Diazepam and Flunitrazepam)

The benzodiazepine diazepam is widely used as anxiolytic, sedative, muscle relaxant and anticonvulsant. It is *N*-demethylated to yield desmethyldiazepam (nordiazepam) and 3-hydroxylated to temazepam.[244,245] CYP2C19 and CYP3A have been identified as the major enzymes responsible for the metabolism of diazepam, and on the basis of *in vitro* data they contribute approximately 33 and 44% to the formation of desmethyldiazepam, respectively, and 9 and 86% towards the production of temazepam, respectively.[161,162,246] The relative contribution of *N*-demethylation and 3-hydroxylation in diazepam metabolism depends on the diazepam concentration used; *N*-demethylation is predominant at low diazepam concentrations.[161,247,248]

Consistent with these *in vitro* studies, it has been reported that diazepam *N*-demethylation cosegregates with (*S*)-mephenytoin hydroxylation polymorphism in Caucasian and Korean individuals.[38,117,142] These findings conflict with the report of Zhang et al.,[77] in which no difference of clearance and half-life of diazepam was found between Chinese PMs and EMs. This discrepancy might derive from recruiting a higher proportion of heterozygous EMs by chance in the Chinese group.[249] In a subsequent study, the same Chinese group of investigators demonstrated that diazepam elimination in Chinese individuals is also highly dependent on CYP2C19 phenotype and genotype.[143,250] Thus, the half-lives of diazepam and desmethyldiazepam (76.2 and 150.7 hours, respectively) of a heterozygous EM individual (*CYP2C19*1/*2*) were longer than those of homozygous EM individuals (20.0 and 91.3 hours, respectively), suggesting a dose-gene effect.[143] As shown in table II, Asian populations have higher proportions of heterozygous EMs and of PMs compared with Caucasian populations.[17] For that reason, the mean clearance of diazepam is lower in Orientals than in Caucasians.[77,249] Of note, many Asian physicians have empirically prescribed smaller doses of diazepam for their patients than the doses recommended for Caucasian patients.[251]

Ethnicity seems to be related to the degree of inhibition of diazepam metabolism by CYP2C19 inhibitors. Caraco et al.[96] compared the effect of omeprazole 40 mg/day for 21 days on diazepam (10mg oral dose) metabolism in Caucasian and Chinese individuals. The findings can be summarised as follows: (i) omeprazole treatment decreased diazepam clearance by 38 and 20.7% in the Caucasian and Chinese groups, respectively; (ii) the AUC of desmethyldiazepam was increased by 42.4% in the Caucasian group and 25.4% in the Chinese group; (iii) the elimination half-lives of diazepam and desmethyldiazepam after administration of omeprazole were significantly greater in the Caucasian group than in the Chinese group; (iv) in the absence of omeprazole, diazepam oral clearance was marginally greater (2.06 *vs* 1.51 L/h, $p = 0.057$) and the AUC of desmethyldiazepam was significantly lower (8794 *vs* 16 358 μg • h/L, $p = 0.04$) in the Caucasian individuals compared with the Chinese individuals. As expected, there was no inhibition of diazepam metabolism by omeprazole in PMs,[83] and the extent of decrease of diazepam clearance by omeprazole was correlated with the baseline clearance of individual EMs.[96]

Drug interactions with diazepam appear to produce no clinically significant outcomes (table VI), in part because of the wide safety margin of diazepam and in part because metabolic pathways catalysed by other enzymes (CYP3A) may operate when CYP2C19 is inhibited. Most inhibitors of CYP2C19 mildly or moderately reduce the clearance of diazepam and prolong its half-life, resulting in minimal or no pharmacodynamic changes. Omeprazole 40 mg/day decreased the clearance of diazepam by 41.8% in Caucasian EMs.[96] Cimetidine, a nonspecific CYP inhibitor, caused a mod-

**Table VI.** Drug interactions of diazepam proposed to be caused by alteration of cytochrome P450 2C19 activity

| Interacting drug | Pharmacokinetic changes | Pharmacodynamic changes |
|---|---|---|
| Omeprazole[96] | 41.8% increase of CL (Caucasian EMs)<br>20.7% increase of CL (Chinese EMs) | NA |
| Omeprazole[83] | 20% increase in $t_{1/2\beta}$ in EMs, with no change in PMs | NS (expected) |
| Omeprazole[222] | 54% decrease of CL, 130% prolongation of $t_{1/2\beta}$ | NA |
| Esomeprazole[99] | 81% higher AUC, 45% lower CL, increase of $t_{1/2\beta}$ from 43 to 86h | NA |
| Cimetidine[252] | 57% higher diazepam and desmethyldiazepam plasma concentration | Minimal |
| Cimetidine[117] | 38% decrease of CL, 39% prolongation of $t_{1/2\beta}$ | NS |
| Cimetidine[256] | 33% decrease of CL, 40-50% increase of plasma concentration | NA |
| Isoniazid[255] | 25.9% decrease of CL, 32.4% prolongation of $t_{1/2\beta}$ | NA |
| Lansoprazole[220] | No | NA |
| Pantoprazole[257] | No | NA |
| Fluoxetine[253] | Decrease of CL and increase of $t_{1/2\beta}$ | NS |
| Fluoxetine[254] | NA | Delirium |
| Sertraline[258] | No | NA |
| Rifampicin (rifampin)[259] | 300% increase of CL, 400% increase of metabolic CL of nordiazepam and 3-hydroxydiazepam, 72.9% decrease of AUC | NA |
| Antituberculosis drugs (isoniazid, rifampicin, ethambutol)[255] | 300% increase of CL and 314% shortening of $t_{1/2\beta}$ | NA |
| Mephenytoin[260] | No change of *S*/*R* ratio by diazepam | NA |
| Amitriptyline[261] | No effect of diazepam | NA |

**AUC** = area under the plasma concentration-time curve; **CL** = clearance; **EM** = extensive metaboliser; **NA** = not available; **NS** = not significant; **PM** = poor metaboliser; $\mathbf{t_{1/2\beta}}$ = elimination half-life.

erate decrease of diazepam clearance (~35%) and increase of half-life (~39%) as well as plasma concentration (>40%) of diazepam and desmethyldiazepam.[252] Fluoxetine, a CYP2C19 and CYP3A inhibitor by its metabolite norfluoxetine, slows the elimination of diazepam.[253,254] Isoniazid also decreases diazepam clearance in healthy individuals.[255] None of these reports found any significant clinical effects of these drug interactions with diazepam, with the exception of one case report describing the development of delirium due to possible drug interaction of diazepam with fluoxetine.[254] Unlike omeprazole, lansoprazole, pantoprazole and rabeprazole have no clinical interaction with diazepam,[220] despite the *in vitro* inhibitory potency of lansoprazole on CYP2C19,[94] and esomeprazole has similar properties in this respect.[99]

Diazepam metabolism is significantly induced by coadministration of rifampicin. Oral clearance of diazepam was increased to 300%, and the formation of desmethyldiazepam and 3-hydroxydiazepam was increased to 400%, by rifampicin.[259] Antituberculosis treatment including isoniazid, rifampicin and ethambutol increased the clearance of diazepam from 0.02 to 0.09 L/h/kg, mainly by rifampicin, despite inhibition of CYP2C19 activity by isoniazid.[255] These data indicate that dosage adjustment of diazepam may be required in patients who are taking both diazepam and rifampicin, and the discontinuation of rifampicin without readjustment of diazepam dosage may cause serious changes in the pharmacokinetics and/or pharmacodynamics of diazepam. However, since rifampicin induces CYP2C19 and CYP3A, and since both are involved in diazepam metabolism, it is difficult to know the degree of induction of CYP2C19-mediated diazepam metabolism.

Generally, CYP2C19-related drug interactions with diazepam seem to have little clinical consequence.[96,117] However, we cannot rule out the

possible development of clinically significant drug interactions of diazepam by high doses of CYP-2C19 inhibitors (e.g. omeprazole), by dual inhibitors (e.g. ketoconazole) or by a combination of a CYP2C19 inhibitor and a CYP3A inhibitor (e.g. erythromycin, ketoconazole, clarithromycin).[262] The development of delirium after a suspected interaction of diazepam with fluoxetine, an inhibitor of both CYP isoforms, might be an example, although the exact mechanism of the interaction was not investigated.[254] Ruffalo et al.[263] also reported that patients receiving the combination of diazepam and cimetidine, a nonspecific inhibitor of both CYP2C19 and CYP3A4, appear to be more sedated than when given an equal dose of diazepam alone. It is recommended to administer oxazepam or lorazepam, benzodiazepines that are eliminated by conjugation, if drug interactions with diazepam are expected to be problematic.

Diazepam itself does not appear to alter the disposition of coadministered drugs. For example, no change in the *S*/*R* ratio of mephenytoin, a marker catalytic activity of CYP2C19 *in vivo*, was found during coadministration of diazepam.[260] Diazepam had no effect on the disposition of amitriptyline.[261]

Flunitrazepam is a widely prescribed hypnosedative benzodiazepine derivative in Europe, whereas its abuse liability is well recognised in North America and other countries. This drug has similar structural, pharmacokinetic and pharmacodynamic properties to diazepam. An *in vitro* human microsomal study by Kilicarslan et al.[148] suggested that flunitrazepam, like diazepam, is *N*-demethylated (main route) and 3-hydroxylated (minor route), primarily by CYP2C19 and CYP3A, respectively. In their discussion, those investigators also mentioned that this is the case *in vivo*, where they claimed to have noted higher plasma concentrations of flunitrazepam (~140%) and greater sedation and psychomotor impairment in CYP2C19-deficient individuals relative to those with full CYP2C19 activity. However, these data are difficult to evaluate as the details of the study and the results were not published.

#### 2.2.2 Phenytoin

Phenytoin, 5,5-diphenylhydantoin (figure 4), has been used for about 60 years as an effective treatment for partial and generalised tonic-clonic seizures, for which it remains the first line of therapy. The metabolism of phenytoin is subject to large interindividual variability, and it is a difficult drug to administer effectively for a variety of reasons that include saturable, nonlinear elimination that is susceptible to dose-dependent change in clearance with age, and a host of possible drug interactions.[108,264,265] Phenytoin is almost completely cleared by hepatic metabolism, with less than 5% of a dose being excreted unchanged. The major and rate-limiting metabolic pathway in humans is stereoselective *p*-hydroxylation of prochiral phenytoin by the CYP system to form (*S*)- and (*R*)- 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH).[108,266]

Studies *in vitro* and *in vivo* clearly indicate that the main enzyme involved in phenytoin clearance is CYP2C9,[126,158] but the activity of this enzyme alone does not appear to explain fully the large interindividual variability in phenytoin clinical pharmacokinetics and the drug interactions reported with phenytoin.[108] Several lines of *in vitro* evidence indicate that CYP2C19 may be involved in phenytoin metabolism. Bajpai et al.[267] have shown that the formation of 4′-HPPH, particularly the (*R*)-isomer, is mainly catalysed by CYP2C19. They also noted that the contribution of CYP2C19 increases with increase in phenytoin concentrations, suggesting that CYP2C19 might be important when CYP2C9 is saturated. Recent studies have further documented the role of CYP2C19 in the primary and secondary metabolism of phenytoin (figure 4).[268]

Since phenytoin has close structural and metabolic similarity with mephenytoin and nirvanol, both of which are substrates of CYP2C19,[9,159] several attempts have been made to link phenytoin metabolism with the activity of CYP2C19 *in vivo*. In 1985, Shimada et al.[269] first reported that the enzyme involved in (*S*)-mephenytoin 4-hydroxylation might also have phenytoin hydroxylase activ-

ity. The first *in vivo* evidence supporting this possibility was provided by Fritz et al.,[126] who noted the association between enantioselective 4′-hydroxylation of phenytoin and the mephenytoin hydroxylation polymorphism in Caucasian individuals. Their findings revealed that (*S*)-4′-HPPH was the major urinary phenytoin metabolite and that this was not different in PMs and EMs of (*S*)-mephenytoin, while the formation of (*R*)-4′-HPPH, which appears a minor pathway,[127] was significantly decreased in PMs of (*S*)-mephenytoin, with a bimodal distribution of the urinary (*S*)-HPPH/(*R*)-HPPH ratio which closely correlated with the (*S*)-mephenytoin hydroxylation index.

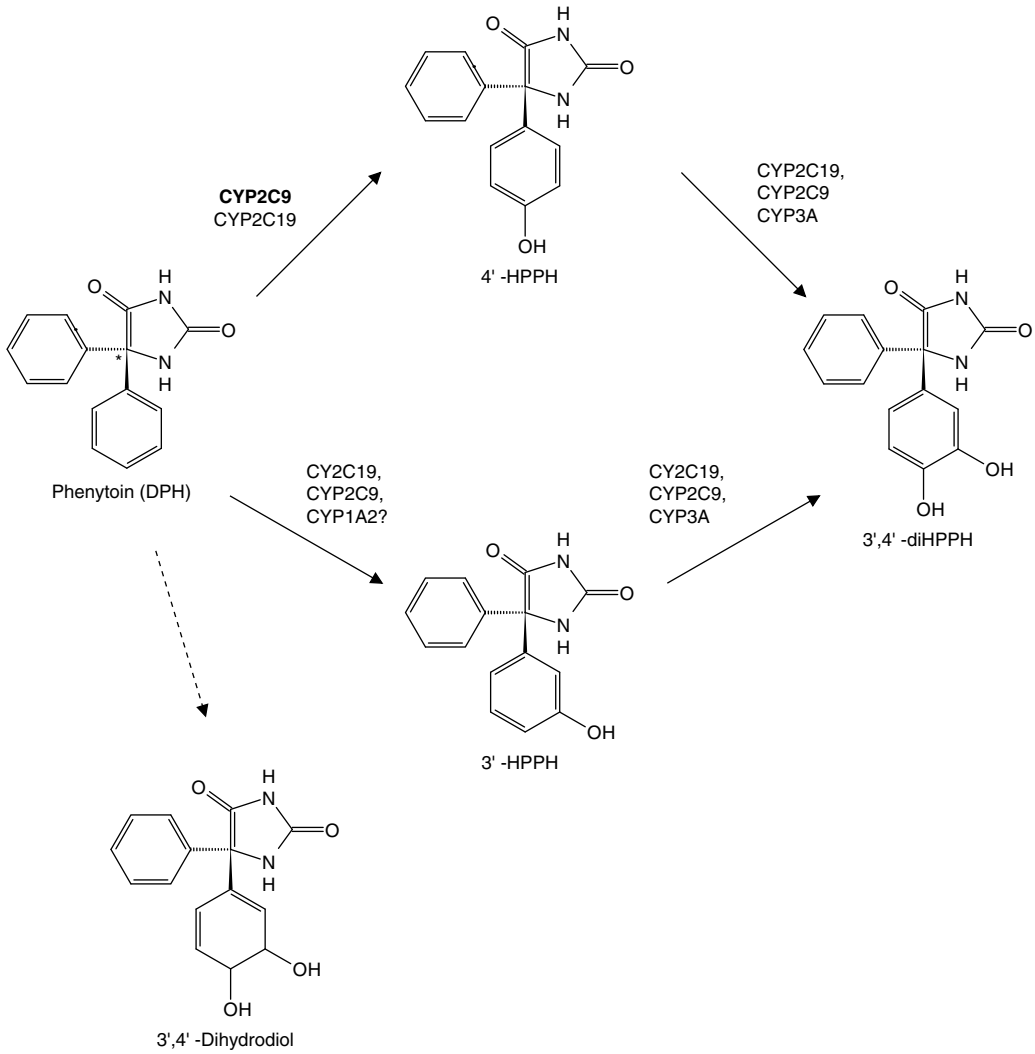


**Fig. 4.** Metabolic pathways of phenytoin and cytochrome P450 (CYP) species involved (reproduced from Komatsu et al.,[158] with permission). **r′-HPPH** = 5-(r′-hydroxyphenyl)-5-phenylhydantoin; **3′,4′-Dihydrodiol** = 5-(3′,4′-dihydroxy-1′,5′-cyclohexadien-1-yl)-5-phenylhydantoin.

Other authors[160] have failed to show any association between phenytoin (100mg single dose) and (*S*)-mephenytoin hydroxylations. The lack of association under this protocol could reflect that the contribution of this enzyme may not be apparent after a single 100mg dose (non-steady-state or nonsaturable plasma concentrations) of phenytoin. Additionally, total urinary metabolites of phenytoin are unlikely to reveal the contribution of CYP2C19 unless chiral analysis of the metabolites formed is performed.

With the development of reliable phenotypic, analytical and genotyping tools to characterise the activities of CYPs *in vivo* and *in vitro*, the impact of CYP2C19 in phenytoin metabolism has been re-examined in recent years. Since the incidence of genetic CYP2C19 variants is known to be more frequent in Orientals, most these studies were done in Japanese healthy individuals and patients with epilepsy. Odani et al.[270] examined the effect of genetic polymorphisms of CYP2C9 and CYP2C19 on the pharmacokinetics of phenytoin in 44 Japanese patients with epilepsy, and noted a modest (~14%) decrease of maximum metabolic rate ($V_{max}$) in individuals with CYP2C19 variants compared to those from homozygous EMs. This impairment was larger if individuals had variants of both CYP2C9 and CYP2C19. Ieiri et al.[127] determined the urinary profiles of (*S*)- and (*R*)-4′-HPPH after oral phenytoin 100mg in Japanese individuals genotyped and phenotyped for CYP2C19, and their findings were essentially similar to observations made earlier in Caucasians individuals.[126] Mamiya et al.,[271] who analysed stereoselective metabolism and population pharmacokinetics of phenytoin in 134 Japanese patients with epilepsy genotyped for CYP2C19, reported an appreciable effect of CYP2C19 on phenytoin metabolism. At a phenytoin dosage of 5 mg/kg/day, the predicted plasma concentrations were 18.7, 22.8 and 28.8 mg/L in homozygous EMs, heterozygous EMs and PMs of CYP2C19, respectively, suggesting a gene dose effect on phenytoin metabolism that is consistent with the pattern observed for other substrates of CYP2C19. They also showed that PMs of CYP2C19 had reduced formation of (*R*)-HPPH. A smaller study[272] investigated the relationship between phenytoin pharmacokinetics and CYP2C19 genotype in 16 Japanese patients and found no difference between genetic (*S*)-mephenytoin PMs and EMs, although $V_{max}$ in patients with the *CYP2C19*3* allele was significantly lower, by 26.4 and 31.6% respectively, than in those with the *CYP2C19*2* or *CYP2C19*1* genotype. However, these data are difficult to understand as both the *CYP2C19*2* and *CYP2C19*3* alleles are associated with complete absence of CYP2C19 activity.

Additional evidence relevant to the role of CYP2C19 in phenytoin metabolism has been obtained from drug interaction studies and clinical case reports in which drugs that are believed to inhibit CYP2C19, but have little or no effect on CYP2C9, increase the plasma concentrations and/or toxicity of phenytoin. Two examples are provided to illustrate this suggestion: phenytoin-ticlopidine and phenytoin-isoniazid clinical interactions.

Phenytoin toxicity associated with elevated plasma concentrations has been described in patients taking ticlopidine. Recently, we[273-275] and others have reported that concomitant administration of ticlopidine elevates plasma concentrations and/or toxicity of phenytoin (reviewed by Ko et al.[107]). Our recent *in vitro* work[107,275] revealed that ticlopidine is at least 60 to 70 times more potent as an inhibitor of CYP2C19 ($K_i$ 1.2 μmol/L) than of CYP2C9 ($K_i$ 86 μmol/L). Ticlopidine would appear to have little clinical effect on CYP2C9 *in vivo*. Gidal et al.[276] determined steady-state warfarin enantiomer concentrations in elderly patients at baseline and after 14 days of treatment with oral ticlopidine 250mg twice daily. They reported that ticlopidine comedication resulted in a significant increase in mean (*R*)-warfarin concentrations (+25.7%, $p < 0.05$), but there was no significant difference in (*S*)-warfarin concentrations (+0.8%). The metabolism of (*R*)-warfarin and (*S*)-warfarin is mediated by CYP2C19[186] and CYP2C9,[266] respectively. Similar

inhibition of CYP2C19 by ticlopidine has been reported *in vitro* by other authors.[277] Recently, Tateishi et al.[105] have studied the effect of ticlopidine 300 mg/day for 6 days on the activity of CYP2C19 in six healthy EM Japanese volunteers, using a single dose of omeprazole 40mg as a substrate probe. Ticlopidine reduced the oral clearance of omeprazole (by 58%) and decreased the ratio of 5-hydroxy-omeprazole to omeprazole (by 71%), essentially confirming the documented *in vitro* data that ticlopidine is a strong inhibitor of CYP2C19. It seems likely that the phenytoin-ticlopidine interaction, documented in the literature, is mediated through inhibition of CYP2C19.

The ability of isoniazid to inhibit the hydroxylation of phenytoin and thereby increase plasma concentrations and toxicity of phenytoin, particularly in slow acetylators of isoniazid, is well documented.[91] Isoniazid has been also reported to slow the elimination of other drugs, including diazepam and primidone,[278] probably by the same mechanism as with phenytoin. To define the possible mechanism of these interactions, we recently tested *in vitro* the inhibitory potency of isoniazid with respect to different CYP isoforms in human liver microsomal preparations.[91] Our data indicated that isoniazid is an inhibitor of CYP2C19-catalysed omeprazole 5-hydroxylation ($K_i$ 25 μmol/L, a therapeutically relevant concentration) with no significant effect on CYP2C9-catalysed flurbiprofen hydroxylation ($K_i$ >500 μmol/L) or tolbutamide methyl hydroxylation ($K_i$ ~102 μmol/L). Thus, the isoniazid-phenytoin clinical interactions documented in the literature are most probably mediated by the ability of isoniazid to inhibit CYP2C19.

Several other drugs appear to increase the plasma concentrations and/or toxicity of phenytoin via inhibition of CYP2C19. Levy et al.[108] surveyed drug interactions with phenytoin and classified the mechanisms of interaction. Of 17 drugs known to elevate plasma concentrations of phenytoin, the effect of only 11 could be explained by mechanisms related to inhibition of CYP2C9, whereas the effects of six of these drugs (omeprazole, felbamate, diazepam, imipramine, fluoxetine and cimetidine) are not consistent with inhibition of CYP2C9. These and other drugs that might influence phenytoin disposition and toxicity

**Table VII.** Drug interactions of phenytoin proposed to be caused by alteration of cytochrome P450 2C19 activity

| Interacting drug | Pharmacokinetic changes | Effects observed |
|---|---|---|
| Ticlopidine[107] | Several case reports and clinical trial showed increased plasma concentrations and decreased CL | Phenytoin toxicity |
| Topiramate[279] | Plasma concentration increased | |
| Omeprazole[280] | No change | None |
| Omeprazole[223] | AUC increased by 25% | None |
| Omeprazole[222] | CL decreased by 15% | None |
| Esomeprazole[99] | 10 to 15% increase in plasma concentration | None |
| Isoniazid[91] | Decreased CL and increased $t_{½β}$ and plasma concentration | Phenytoin toxicity |
| Cimetidine[108,264] | CL reduced by 15-20%, plasma concentrations increased by 13-60% | Minimal |
| Felbamate[84,108] | 33 to 67% increase of plasma concentrations with felbamate 1200 and 1800 mg/day, respectively | Phenytoin toxicity |
| Felbamate[281] | 22 and 33% decrease of CL with felbamate 1200 and 1800 mg/day, respectively | NA |
| Fluoxetine[108] | Plasma concentrations increased by >2-fold | Phenytoin toxicity |
| Zonisamide[110,282] | Increased $K_m$ of phenytoin by 16% | |
| Viloxazine[283] | Plasma concentrations increased by average of 37% (range 7-94%) after addition of viloxazine 150-300 mg/day for 21 days | |

**AUC** = area under the plasma concentration-time curve; **CL** = clearance; **$K_m$** = Michaelis constant; **NA** = not available; **$t_{½β}$** = elimination half-life.

through inhibition of CYP2C19 are summarised in table VII.

All *in vitro* and clinical data provide unequivocal evidence that CYP2C19 is involved in the metabolism of phenytoin. Two important questions remain: why does inhibition of CYP2C19, which appears to be a 'minor' pathway of phenytoin metabolism, cause clinically relevant effects and when does CYP2C19 become an important determinant of phenytoin elimination and/or toxicity? It is possible that the answer to these questions lie in the nonlinear elimination nature of phenytoin and its narrow therapeutic range. Recently, Donahue et al.[275] estimated the *in vivo* inhibition of phenytoin metabolism by ticlopidine to be 15 and 34% at ticlopidine concentrations of 1 and 3 μmol/L, respectively, while the inhibition of the CYP2C9-mediated metabolism was predicted to be below 1%. The fractional contribution of CYP2C19 to overall phenytoin metabolism appears to increase with increasing phenytoin concentrations. The point at which the saturation occurs is unpredictable and probably varies among patients, but this may occur even at low concentrations (8 mg/L) in some patients. Bajpai et al.[267] reported different $K_m$ values for CYP2C9-catalysed (5.5 μmol/L) and CYP2C19-catalysed (71.4 μmol/L) phenytoin hydroxylation *in vitro*, suggesting that the CYP2C9 pathway is likely to become saturated at therapeutic steady-state plasma concentrations of phenytoin (40 to 80 μmol/L).[127] They predicted that the contribution of CYP2C19 would increase 3-fold between 5 and 60 μmol/L phenytoin. Consistent with these findings, the ratio of (*S*)-HPPH to (*R*)-HPPH has been reported to be higher in PMs of CYP2C19 or lower during repeated administration than after a single dose.[126] The shift in the enantiomeric ratio under different conditions may reflect the relative activity of CYP2C19 and CYP2C9. Patients who are heterozygous for the Leu359 variant of CYP2C9 showed saturation of phenytoin hydroxylation at relatively low dosage compared to those with CYP2C19 variants, whereas the impact of genetic variants of CYP2C19 is greater at higher phenytoin dosages.[127] It is possible that, once the CYP2C9-mediated metabolism of phenytoin is saturated, the role of CYP2C19 increases, and a minor interference with this enzyme then produces clinically significant interactions and provides an explanation for the increased risk of phenytoin clinical toxicity during coadministration of drugs that inhibit CYP2C19. Individuals heterozygous or homozygous for *CYP2C9*2* and *CYP2C9*3* (particularly Caucasians) will show significant impairment of phenytoin hydroxylation.[284] Approximately 1 to 2% of Caucasians will have both impaired CYP2C9 and complete absence of CYP2C19, and these individuals may particularly be susceptible to adverse events associated with phenytoin use.

#### 2.2.3 Barbiturates (Hexobarbital, Mephobarbital and Phenobarbital)

Barbiturates are widely used as hypnosedatives, anticonvulsants and for induction of anaesthesia. An increase in dose or concentration of these drugs above that needed for hypnosis may lead to important CNS adverse effects, including respiratory depression and coma. For drugs such as phenobarbital that have long half-lives (days), there is also a risk of accumulation during repeated administration.

Recent evidence suggests that CYP2C19 is involved in the *p*-hydroxylation of phenobarbital, one of the frequently used barbiturates in its own right and an active metabolite of other drugs (e.g. primidone and mephobarbital). In a clinical case report, addition of felbamate 50 mg/kg, a known CYP2C19 inhibitor,[84,285,286] to a patient who was on phenobarbital 200 mg/day increased the plasma phenobarbital concentration from 48 to 68 mg/L associated with clinically significant neurotoxicity.[287] In healthy volunteers, felbamate has been reported to increase the AUC and $C_{max}$ of phenobarbital by 22 and 24%, respectively.[288] Mamiya et al.[164] analysed the population pharmacokinetics of phenobarbital in 74 Japanese epileptic patients genotyped for CYP2C19 and showed that PMs had lower mean clearance (18.8%) than heterozygous EMs and homozygous EMs. They suggested that the estimated population clearance val-

ues in the three genotypes might help to determine the phenobarbital dosage required to achieve an appropriate plasma concentration in an individual patient. Recently, the same investigators have compared the pharmacokinetics of phenobarbital in six EMs and six PMs of CYP2C19.[129] They confirmed that the *p*-hydroxylation of phenobarbital cosegregates with CYP2C19 activity, as the formation clearance and urinary excretion of this metabolite respectively were ~40 and 30% lower in PMs than in EMs of CYP2C19. In contrast to their earlier study,[164] however, kinetic parameters of the parent drug was not significantly different among EMs and PMs, although a trend towards slowed elimination was noted in PMs > heterozygous EMs > homozygous EMs.

In order to understand the contribution of CYP2C19 to phenobarbital metabolism, other factors that are involved in phenobarbital clearance should be understood. Only 40% of the *p*-hydroxylation pathway is accounted for CYP2C19, while about 60% seems to be catalysed by other enzymes.[129] Only 7.7 to 12.5% of the dose is excreted as *p*-hydroxyphenobarbital.[129] It follows that other elimination routes such as *N*-glucuronidation and renal excretion (~27% of the dose) are quantitatively important in the remaining fraction and for the overall elimination of phenobarbital in humans. The consequences of impaired phenobarbital elimination include increased adverse effects (e.g. drowsiness) or, because long-term administration of barbiturates is known to induce several drug-metabolising enzymes, accumulation of phenobarbital that may produce greater induction of the metabolism of coadministered drugs and endogenous substances, such as bilirubin and vitamin D. However, alternative elimination pathways in addition to CYP2C19 metabolic status should be evaluated to predict phenobarbital disposition and response.

CYP2C19 is also involved in the metabolism of other barbiturates such as hexobarbital and mephobarbital. According to Knodell et al.,[121] CYP2C19 purified from human liver efficiently catalyses 3′-hydroxylation of hexobarbital. *In vivo*, after oral administration of hexobarbital 300mg, they noted increased hexobarbital concentrations and a decrease of its plasma and urinary metabolites in PMs compared with EMs of CYP2C19, together with more marked sedation in PMs than EMs.[121] A further *in vitro* study by Yasumori et al.[165] in liver microsomes from Japanese donors showed that oxidation of (*R*)- and (*S*)-hexobarbital is faster in EMs than in PMs. Adedoyin et al.[122] have studied the disposition of (*R*)- and (*S*)-hexobarbital in Chinese and Caucasian PMs and EMs of CYP2C19 and provided strong evidence that the major routes of hexobarbital metabolism in humans are mediated by CYP2C19. They found that: (i) the oral clearance of both enantiomers was lower in PMs than in EMs; (ii) the oral clearance of (*R*)-hexobarbital was 5- to 6-fold greater than that of (*S*)-hexobarbital, whereas (*S*)-hexobarbital was eliminated twice as fast as (*R*)-hexobarbital in PMs; and (iii) the formation of all the human metabolites identified from both isomers cosegregated with the activity of CYP2C19.

Similar results were obtained with regard to the metabolism of mephobarbital. Kupfer and Branch[166] measured the 8-hour urinary recovery of 4-hydroxy-mephobarbital after oral administration of racemic mephobarbital 90mg in 17 EMs and six PMs (phenotyped with mephenytoin) and found that the recovery of this metabolite contributed ~11% of the total dose of mephobarbital in EMs without a detectable amount in PMs. Mephobarbital metabolism *in vivo* in humans appear to be stereoselective in that the (*R*)-isomer is more efficiently metabolised than the (*S*)-isomer,[166] and this was supported by recent *in vitro* microsomal data by Kobayashi et al.,[167] who showed that the 4-hydroxylation of mephobarbital exclusively catalysed by CYP2C19 is preferential for the (*R*)-enantiomer. Of note, the frequency of CNS adverse effects of mephobarbital has been reported to be 6-fold higher (~20%) in Japanese individuals[35] than in Europeans living in Australia (3.5%),[13] and this difference was attributed to the higher frequency of the PM trait in Orientals than in Caucasians.

Taken together, the metabolism and pharmacokinetics of certain barbiturates (phenobarbital, mephobarbital and hexobarbital) have been shown to depend on the activity of CYP2C19. It is not surprising that the incidence of adverse CNS reactions to these drugs is more frequent in PMs relative to EMs, and in Orientals relative to Caucasians, but, with the exception of phenobarbital, other safer drugs have largely replaced these agents.

#### 2.2.4 Carisoprodol

Carisoprodol is a centrally acting muscle relaxant and analgesic that is an effective adjunct in the treatment of acute musculoskeletal disorders. Carisoprodol is extensively metabolised in the liver.[289] *N*-Demethylation to meprobamate, a commercially available anxiolytic agent in its own right, seems to represent about 84% of the oral clearance of the drug.[168] The first evidence that this metabolic pathway might be under the control of genetic polymorphism of CYP2C19 was provided in a study by Olsen et al.[168] in which carisoprodol 700mg as a single oral dose was extensively converted to meprobamate in nine healthy volunteers with a short mean half-life (99 ± 46 min), while one individual who was a PM of mephenytoin had a long half-life (376 min), with only small amounts of meprobamate detected in plasma. A subsequent study by Dalen et al.[169] reported the clearance of carisoprodol to be 4-fold lower in PMs than in EMs of CYP2C19. PMs of CYP2C19 might be at greater risk for carisoprodol-induced drowsiness, the most frequently occurring adverse effect (seen in up to 40% of patients receiving the drug), and thus be susceptible to accidents from impaired driving. Because its therapeutic benefit might be due to meprobamate, and since this metabolite is present in high concentrations (15 to 25 μmol/L) in plasma after the administration of carisoprodol to EMs of CYP2C19,[168] it is possible that the therapeutic effect of carisoprodol is diminished in patients who are PMs of CYP2C19, but it is not clear whether this active metabolite alone is responsible for the therapeutic effect of carisoprodol.

### 2.3 Antidepressants

CYP2C19 is involved in the *N*-demethylation of the tertiary amine tricyclic antidepressants (TCAs) imipramine,[290] amitriptyline,[291] trimipramine[180] and clomipramine,[292] and of the secondary amine TCA nortriptyline.[182] In addition to CYP2C19, CYP1A2 and CYP3A4 are also known to be involved in the same metabolic pathway of these drugs *in vitro*,[182,290,291,293-295] though their contribution to *in vivo N*-demethylation of TCAs is not well demonstrated, due in part to inadequate *in vivo* functional tests for these isoforms.[296] The hydroxylation pathway is mediated mainly by CYP2D6.[297] Although multiple CYP isoforms are involved in the metabolism of these antidepressants, the plasma concentrations of these drugs and their active metabolites have been reported to be greater in PMs than in EMs of CYP2C19.[175,298,299]

TCAs have very narrow therapeutic ranges, and their therapeutic efficacy and toxic effects are well known to be associated with the plasma concentration.[300,301] Therefore, the development of adverse effects would be expected to be higher in PMs of CYP2C19. However, several studies have failed to demonstrate a direct association between CYP2C19 genetic polymorphism and the adverse effects of TCAs, including seizure and myoclonus, due in part to inadequate study design and a small number of individuals.[299,302]

Compared with CYP2C19, CYP2D6 polymorphism appears to be more important to the plasma concentration of antidepressants and their clinical effects. Several reports have described concentration-dependent adverse effects in PMs of CYP2D6 treated with the usual therapeutic dosages of TCAs.[303] Koyama et al.[178] reported that CYP2D6 polymorphism has more effect than CYP2C19 on the AUC of desipramine after a single dose of imipramine. Imipramine concentrations were 1.5-fold higher in CYP2D6 PM/CYP2C19 EM and CYP2D6 EM/CYP2C19 PM compared with CYP2D6 EM/CYP2C19 EM, and desipramine concentrations were around 10-fold higher in CYP2D6

PM/CYP2C19 EM and 40% lower in CYP2D6 EM/CYP2C19 PM.

Severe adverse effects of TCAs appear especially likely when both metabolic pathways are blocked. For example, severe adverse effects have been observed after concomitant administration of a TCA with fluvoxamine or fluoxetine, inhibitors of both CYP2C19 and CYP2D6.[304] Similar effects are expected when CYP2C19 inhibitors (e.g. omeprazole)[94] or CYP2D6 inhibitors (e.g. quinidine and many antipsychotics)[305] are coadministered with tertiary amine TCAs in CYP2D6 PMs and CYP2C19 PMs, respectively. As with diazepam, considerably lower dosages of antidepressants, including TCAs, have been prescribed empirically in East Asians compared with Caucasians.[306] This practice seems to be derived, at least in part, from the pharmacogenetic differences between the two ethnic groups in both CYP isoforms involved in the metabolism of these drugs. Compared with about 3% of CYP2C19 PMs among Caucasians, the proportion of CYP2C19 PMs in Asians is as high as 15 to 20%.[37,307] The mean CYP2D6 activity is also lower in Asians than Caucasians because of the higher proportion of the *CYP2D6*10* mutation, which yields lower enzyme activity, in Asians.[37,308]

Some of the selective serotonin reuptake inhibitors (SSRIs), such as citalopram, sertraline, fluoxetine and venlafaxine, and the reversible MAO inhibitor moclobemide are also substrates of CYP2C19 (table IV). According to Wang et al.,[150] the mean clearance of sertraline was decreased (~30%) and the AUC and half-life were increased by ~41% and ~51%, respectively, in Chinese CYP2C19 PMs compared with EMs, whereas the mean AUC (~36%) and $C_{max}$ (~27%) of *N*-desmethyl-sertraline were lower in PMs than in EMs. In two of their PMs (but not EMs), they noted severe gastrointestinal disturbances and increased CNS effects (dry mouth and dizziness) 2 hours after sertraline administration. Recently, Liu et al.[149] have demonstrated that CYP2C19 plays a major role in *N*-demethylation of fluoxetine (single oral 40mg dose) to norfluoxetine in Chinese individuals. They found a significant mean increase of 46, 128 and 113% in $C_{max}$, AUC and half-life, respectively, and a 55% decrease in clearance of fluoxetine in Chinese PMs compared with EMs. The AUC of norfluoxetine was significantly higher in EMs than in PMs. A study by Sindrup et al.[174] indicated that the AUC, half-life and $C_{max}$ of racemic citalopram (40 mg/day for 10 days) were significantly higher in PMs of CYP2C19 than in EMs, whereas total clearance and formation clearance of desmethyl-citalopram were ~44% and ~56% lower in PMs than in EMs. CYP2D6 and CYP2C19 have been implicated in the metabolism of venlafaxine, a new antidepressant that blocks the reuptake of serotonin, noradrenaline and dopamine, to *O*-desmethyl-venlafaxine, which is a major metabolic pathway and an active metabolite. There is also evidence that moclobemide is a substrate of CYP2C19 *in vitro*,[100] which was later confirmed from a study by Yu et al.,[309] who reported significantly slower elimination of moclobemide in PMs than in EMs of CYP2C19, as well as during administration of single (40mg) and multiple (40 mg/day for 7 days) doses of omeprazole to EMs.

Drug interactions of antidepressants are important because these drugs are frequently combined with many other drugs such as antipsychotics,[310] have a narrow therapeutic range (e.g. TCAs) and may cause serious adverse effects associated with increased drug concentrations. Table VIII summarises drug interactions of antidepressants related to CYP2C19 substrates. Cimetidine, a nonspecific CYP inhibitor, increases the plasma concentrations of the reversible MAO inhibitor moclobemide and of tertiary amine TCAs, but not of secondary amine TCAs.[311] TCAs appear not to strongly inhibit the metabolism of CYP2C19 substrates. They have no interaction with mephenytoin and moclobemide.[311] However, it should be considered that minor inhibition by imipramine has been reported to significantly increase the plasma concentration of phenytoin, which has saturable pharmacokinetics and is metabolised mainly by CYP2C9 and partly by CYP2C19,[108,312] even though

**Table VIII.** Drug interactions of antidepressants related to cytochrome P450 2C19

| Interacting drug | Affected drug | Changes observed |
|---|---|---|
| Cimetidine[313] | Imipramine | Increase of imipramine and desipramine concentrations, decreased after discontinuation of cimetidine |
| Cimetidine[314] | Imipramine, nortriptyline | 40% increase in AUC. No significant change |
| Cimetidine[315] | Amitriptyline | 80% increase in amitriptyline AUC, decrease in nortriptyline concentration |
| Cimetidine, amitriptyline, desipramine[311] | Moclobemide | 100% increase in moclobemide concentration, no clinical interaction |
| Cimetidine[316] | Moclobemide | 52% decrease in oral CL |
| Imipramine[312] | Phenytoin | Increase in plasma phenytoin concentration, mild signs of phenytoin intoxication (drowsiness, incoordination, behavioural change) |
| Fluvoxamine[317] | Clomipramine | 4-fold increase in clomipramine concentration, 43% decrease in desmethylclomipramine concentration |
| Fluvoxamine[90] | Chloroguanide | 39% decrease in chloroguanide CL, 85% decrease in cycloguanil formation |
| Fluvoxamine[318] | Clomipramine | 2.4-fold increase in clomipramine concentration, decrease in desmethyl- and 8-hydroxyclomipramine, myoclonic jerk and EEG change in 2 patients (9% of 22 patients) |
| Fluvoxamine[319] | Citalopram | 3.1- and 1.8-fold increases in (*S*)- and (*R*)-citalopram, increase in *S*/*R*-citalopram from 0.48 to 0.84, clinical improvement in 50% of patients |
| Fluoxetine[320] | Imipramine 125mg | Toxic concentrations of imipramine (1450 nmol/L) and desipramine (680 nmol/L) |
| Fluoxetine[321] | Imipramine, desipramine | 71.8% decrease in imipramine CL, 90.7% decrease in desipramine CL |
| Fluoxetine [322] | Moclobemide | Increase in moclobemide AUC, no serotonin syndrome |
| Fluoxetine[323] | Amitriptyline | Death, probably due to drug interaction |
| Amylobarbitone[324] | Imipramine | Decreased imipramine concentration (80%) and increased desipramine concentration (20%) [total concentration of imipramine and desipramine, 40% decrease] |
| Butalbital[325] | Imipramine | 50% decrease in imipramine concentration |

**AUC** = area under the plasma concentration-time curve; **CL** = clearance.

the mechanism of this interaction remains to be evaluated.

Fluvoxamine, fluoxetine and moclobemide are inhibitors of CYP2D6, CYP3A4, CYP1A2 and CYP2C19,[85,90] all CYP isoforms reported to be involved in the metabolism of antidepressants, including tertiary amine TCAs.[100,182,290-292,294,326,327] Fluoxetine and fluvoxamine, for example, markedly increase the plasma concentrations of all known CYP2C19 substrate antidepressants, including tertiary TCAs, citalopram and moclobemide, which may cause serious adverse effects.[317] Therefore, it is recommended to start with small doses of these antidepressants when they are added to fluoxetine or fluvoxamine, or switched from fluoxetine. Drug interactions of SSRIs and TCAs and their clinical outcomes were thoroughly reviewed by Taylor in 1995.[328]

On the basis of available clinical data, Kirchheiner et al.[329] recently recommended dosage reductions of amitriptyline, citalopram, clomipramine, imipramine, moclobemide and trimipramine by 30% to 60% in PMs compared with EMs of CYP2C19. Given the narrow therapeutic range of TCAs, CYP2C19 genetic polymorphism is likely to have particularly important safety implications for this class of drugs as compared with the SSRIs and moclobemide, which are relatively better tolerated. Patients who are PMs of CYP2D6 and CYP2C19 seem to be at particularly high risk of adverse effects. In linking genotype with pharmacokinetics and response of antidepressants, it is necessary to take the role of active metabolites into account, particularly since the metabolism of certain drugs (e.g. imipramine, amitriptyline, clomipramine and fluoxetine) leads to pharmacologically active metabolites[329] and because CYP2C19

may participate in the elimination of the parent and/or the metabolite.

## 2.4 Anti-infectives

### 2.4.1 Proguanil

Proguanil and chlorproguanil are antimalarials that are important prophylactic agents in East Africa and Southeast Asia, where chloroquine-resistant strains of *Plasmodium* are found. These drugs are prodrugs that undergo CYP- mediated biotransformation to their respective active triazine metabolites, cycloguanil and chlorcycloguanil.[330] That this activation pathway may be under the control of a genetic polymorphism was first suggested by Helsby et al.,[144] who noted that the urinary proguanil/cycloguanil ratios in a population study exhibited high interindividual variability. Subsequent *in vitro* studies have identified that these biguanides are activated by CYP2C19.[171] Accordingly, studies in healthy volunteers have demonstrated that the urinary metabolic ratio of the biguanides correlates with the activity of CYP2C19 as measured *in vivo* by specific substrate probes,[41,170] and hence the conclusion that the pharmacokinetic variability observed[144] is attributed to CYP2C19 genetic polymorphism. According to Hoskins et al.,[69] a CYP2C19 gene-dose-effect for proguanil oxidation has been demonstrated. Further, known CYP2C19 inhibitors/-substrates, including fluvoxamine,[90] omeprazole,[98] (*S*)-mephenytoin[171] and cimetidine,[82] have been reported to decrease the formation of cycloguanil from proguanil *in vivo* and *in vitro*. Thus, it is not surprising that proguanil has been tested as an *in vivo* probe to phenotype CYP2C19 in different populations.[41,50,69]

If a drug requires metabolic activation before it has any effect, then the clinical consequences of impaired metabolism due to genetic polymorphism may be significant. A typical example in this respect is the loss of analgesic effect of codeine in poor metabolisers of CYP2D6, due to deficient conversion of codeine to its pharmacologically active metabolite morphine.[331] The potential clinical interest in the relationship between CYP2C19 activity and the bioactivation of biguanides depends on answering a number of questions. Are the antimalarial actions of these drugs solely mediated by the formation of active metabolites? How important is CYP2C19 quantitatively in the activation of biguanides? Will patients who are PMs of CYP2C19 or those taking other drugs that inhibit this isoform produce subinhibitory concentrations of the active molecules, such that increased risk of treatment or prophylactic failure and emergence of parasite resistance occur in a fairly large number of people living in or travelling to malaria endemic areas? The answers to these questions seem to be not straightforward.

Skjelbo et al.[57] reported that CYP2C19 metabolic status expressed by the *S*/*R* mephenytoin ratio did not correlate with the number of malaria breakthrough parasitaemia episodes in Tanzanian patients, whereas a weak but significant correlation was found when proguanil/cycloproguanil ratio was considered. The antimalarial activity *ex vivo* of plasma samples obtained from Thai EMs and PMs given proguanil was studied using isolated *P. falciparum*,[332] but, despite the clear difference in pharmacokinetic parameters between EM and PM individuals, no difference was observed with respect to the antimalarial effect of proguanil *in vitro* between the groups. In agreement with these data, Kaneko et al.[333] have recently studied the relationship between CYP2C19 genotype and proguanil metabolism in 100 patients with uncomplicated malaria in Vanuatu, and showed that PMs of CYP2C19 had higher plasma concentrations of proguanil, lower plasma concentrations of cycloguanil and 4-chlorophenylbiguanide and more gastrointestinal adverse reactions, but there was no difference in the incidence of malaria between the two groups.

Two possibilities can be suggested to explain why CYP2C19 phenotypes or genotypes have failed to be good predictors of antimalarial activity. First, all PMs of CYP2C19 had detectable levels of active metabolites *in vivo*,[57,334] which could be due to the involvement of other isoforms (e.g. CYP3A) in the activation of proguanil.[172] It may

be possible that, although CYP2C19 activity is absent, clinically relevant concentrations of the active metabolite are produced by CYP3A in individuals who are PMs of CYP2C19. This is probably also the reason why, regardless of the excellent concordance between the mephenytoin phenotype and proguanil phenotype, several authors have observed that the proguanil/cycloguanil ratio does not fully reflect CYP2C19 activity in the same manner as mephenytoin hydroxylation index.[144] Secondly, the parent compounds might have significant intrinsic efficacy against malaria, independent of the active metabolites. A recent study by Kaneko et al.[335] revealed that the antimalarial efficacy of proguanil is the same in both EMs and PMs of CYP2C19, despite the fact that plasma concentrations of cycloguanil could be detected significantly more often in EMs than in PMs, suggesting that the parent drug itself possesses significant intrinsic efficacy against malaria independent of the metabolite cycloguanil. Together, current data do not support that the activation of proguanil is critical to its antimalarial effect.

#### 2.4.2 Nelfinavir

The antiretroviral drug nelfinavir is converted to an active metabolite (M8)[336] by CYP2C19 *in vitro* as well as *in vivo*.[134,145] Acquired CYP2C19 deficiency from moderate or severe liver disease[134] or from concurrently administered CYP-2C19 inhibitor drugs (e.g. omeprazole)[337] appears to moderately diminish the formation of M8 in patients with HIV infection.[134] However, since the parent and the active metabolite appear to have similar antiviral activity, overall efficacy may not differ between EMs and PMs of CYP2C19.

### 2.5 Miscellaneous Drugs

#### 2.5.1 Tolbutamide

Tolbutamide is an oral hypoglycaemic agent used in the treatment of type 2 diabetes mellitus. The drug undergoes extensive hepatic CYP-mediated hydroxylation of the methyl group attached to the phenyl moiety, which is the first and rate-limiting step in its metabolism, accounting for over 85% of the tolbutamide dose in humans.[266,338] Because hepatic extraction of tolbutamide is low, variability in its clearance should be explained by interindividual variability in the CYP system. The main CYP isoform responsible for the elimination of this drug is CYP2C9, and for that reason this drug is a useful *in vitro* and *in vivo* probe of CYP2C9.[266,339]

In addition to CYP2C9, there is also evidence that implicates CYP2C19 in the methyl hydroxylation of tolbutamide. This conclusion derives primarily from *in vitro* studies involving human liver microsomes or recombinant enzymes.[185,338] Using human recombinant enzymes, we have recently demonstrated that tolbutamide methyl hydroxylation is catalysed by CYP2C19[340] and inhibited by isoniazid and ticlopidine,[91,107] which are potent CYP2C19 inhibitors. Lasker et al.[185] compared the metabolism of tolbutamide by purified and reconstituted CYP2C19 and CYP2C9. They found that CYP2C19 is an efficient catalyst of tolbutamide metabolism, exhibiting essentially similar turnover, kinetic parameters ($V_{max}$ and $K_m$) and inhibition profiles to those of CYP2C9 when calculated on a haem basis. Consistent with these findings, we found that both recombinant human CYP isoforms exhibit similar kinetic parameters (similar *in vitro* intrinsic clearance, expressed by $V_{max}/K_m$), marking the participation of CYP2C19 and CYP2C9 with similar affinity for tolbutamide.[340] Of note, the Eadie-Hofstee plot of tolbutamide metabolism is consistent with monophasic kinetics.[185,340] Based on *in vitro* data, the contribution of CYP2C19 to tolbutamide metabolism has been estimated to range from 14 to 22%.[341]

Evidence *in vivo* for the involvement of CYP2C19 in the metabolism of tolbutamide concurs with these *in vitro* data. Knodell et al.[338] have shown a significant correlation between tolbutamide and (*S*)-mephenytoin hydroxylations *in vitro*, but plasma tolbutamide concentrations were similar in PMs and EMs of mephenytoin, whereas the tolbutamide/4-hydroxy-tolbutamide ratio in the urine was significantly higher in PMs than in EMs. Although it did not reach a statistically significant

level, Shon et al.[342] have observed the same trend in healthy Korean volunteers.

It may be that the relative amount of CYP2C19 to CYP2C9, in which the former represents about 1% and the later about 20% of total CYP,[343] precludes an important role for CYP2C19 in hepatic tolbutamide metabolism and any polymorphism thereof. Clearly, CYP2C9 remains the major enzyme responsible for the clearance of tolbutamide but, given the narrow therapeutic range of tolbutamide, CYP2C19, analogous to its role in phenytoin clearance (section 2.2.2), might play a role in tolbutamide elimination in certain patients (e.g. individuals expressing either high levels of CYP2C19 or a catalytically deficient CYP2C9 enzyme). In particular, the metabolic clearance of tolbutamide as well as of its metabolite, and the corresponding consequences for blood glucose control, need to be investigated in individuals with unusual metabolic characteristics with respect to the activity of CYP2C19 and CYP2C9. This may have significance not only for tolbutamide, but also for the metabolism of chemically related first- and second-generation oral hypoglycaemics and other structurally similar agents (e.g. toresamide).

Apart from the possible clinical implications of the involvement of CYP2C19 in the pharmacokinetics of tolbutamide, it is likely that the involvement of CYP2C19 in tolbutamide metabolism will greatly diminish the utility of tolbutamide as a probe for CYP2C9, particularly when inhibitors that are potent and selective for CYP2C19 (e.g. ticlopidine) are evaluated in human liver microsomal preparations that have diminished CYP2C9 activity and high CYP2C19 activity.

#### 2.5.2 Propranolol

The β-blocker propranolol is extensively metabolised by the hepatic CYP system. Although its contribution to the overall clearance of propranolol is not clear, the side-chain oxidation of propranolol to form naphthoxyl-acetic acid has been shown to cosegregate with (*S*)-mephenytoin hydroxylation index.[184] On the other hand, Xie et al.[344] did not find a significant relationship between the partial metabolic clearance of propranolol to naphthoxyl-acetic acid and the 8-hour urinary *S*/*R* ratio of mephenytoin in Chinese individuals. Because of the involvement of multiple pathways and multiple CYP isoforms in propranolol metabolism, the clinical effect of modifying CYP2C19 activity due to chemical inhibition or genetic polymorphism appears to be minimal.

#### 2.5.3 Other Drugs

Indirect evidence suggests that the metabolism of terodiline, an anticholinergic drug that has been used to treat urinary incontinence due to detrusor instability, might be under the control of CYP2C19 activity. The drug was withdrawn from the market because of its ability to prolong QTc interval and induce torsade de pointes. Recently, Ford et al.[345] have suggested that possession of the *CYP2C19*2* allele might be a risk factor for terodiline cardiotoxicity, but direct *in vitro* or *in vivo* evidence that implicates CYP2C19 in the metabolism and thus cardiotoxicity of this drug is lacking.

The oral anticoagulant warfarin is administered as a racemic preparation. Multiple CYP isoforms, including CYP2C19, appear to be involved in the 8-hydroxylation pathway of (*R*)-warfarin.[186,346] However, inhibition or genetic polymorphism of CYP2C19 is unlikely to have any significant effect on the total clearance of warfarin and particularly on its anticoagulant effect, as (*S*)-warfarin is pharmacologically more active than (*R*)-warfarin and metabolism of the (*S*)-enantiomer is mainly catalysed by CYP2C9.[266]

CYP2C19 has been implicated in thioridazine metabolism *in vivo*,[183] but its contribution to the safety and efficacy of this drug has not yet been determined. Thioridazine is mainly metabolised by CYP2D6. Any role of CYP2C19 in the elimination of this drug is expected to be small.

A number of *in vitro* studies implicate CYP2C19 in the metabolism of several other drugs and endogenous compounds (see table IV), but since extrapolation to the *in vivo* situation from *in vitro* data alone is difficult, further study may be needed to demonstrate the significance of CYP2C19 genetic polymorphism in the metabolism of these agents.

### 3. Association of CYP2C19 Genotype with (Xenobiotic-Induced) Disease

The consequences of CYP2C19 inhibition and genetic polymorphism with respect to the safety of CYP2C19 substrate drugs have been discussed in sections 1 and 2. A number of studies have attempted to define a relationship between CYP2C19 genotype and xenobiotic-induced disease.

There are reports of an association between CYP2C19 activity and certain forms of cancer. In 1987, Kaisary et al. reported a weak association between nonaggressive bladder cancer and high CYP2C19 activity,[347] although other authors did not reveal any association.[348] Tsuneoka et al.[349] demonstrated that Japanese PMs had increased risk of lung cancer, particularly with squamous cell carcinoma. Brockmöller et al.[350] reported that increased CYP2C19 activity is a risk factor for bladder cancer. Roddam et al.[351] genotyped for CYP2C19 over 550 cases of acute leukaemia and 950 matched controls in a population-based case-control study and found a nonsignificant relationship between increased risk of leukaemia and CYP2C19 PM genotype (odds 1.68, 95% confidence interval 0.97 to 2.92). Chau et al.[352] conducted a study in 38 patients with cirrhosis to assess whether the frequency of CYP2C19 alleles differed in 38 Japanese cirrhotic patients who developed hepatocellular carcinoma and found that, among 24 hepatitis C virus-seropositive patients with cirrhosis and hepatocellular carcinoma, the PM phenotype frequency was 41.7%, significantly higher than that observed in 186 healthy controls. They concluded that PM phenotype caused by the variation of CYP2C19 gene in cirrhotic patients with HCV infection is associated with a high risk for developing hepatocellular carcinoma.[352]

One study[353] reported an association between drug-induced adverse hepatotoxicity and PMs of mephenytoin. Patients with hepatitis induced by a mixture of phenobarbital, febarbamate and defebarbamate had a higher mean hydroxylation index ($12.4 \pm 8.3$) compared with healthy controls ($1.8 \pm 0.4$) or patients with other drug-induced hepatitis ($2.5 \pm 3.3$). CYP2C19 deficiency has been reported to be associated with incidence of scleroderma.[354] Helsby et al.[355] have reported a preponderance of PMs of CYP2C19 (50%) in patients with severe psoriasis compared to those with mild psoriasis or control individuals. PMs of CYP2C19 appear to have diminished stated preferences for spinach and cabbage.[356] No association was found between CYP2C19 genetic polymorphism and Parkinson's disease, chronic liver failure, lung cancer, prostate cancer, idiopathic systemic lupus (see review[19]) or human longevity.[64]

*In summary*, there are occasional reports that suggest an association of the CYP2C19 genetic polymorphism with certain diseases, but all these studies are descriptive in nature and they do not provide mechanisms (e.g. substrates activated) to relate variations in CYP2C19 enzyme with any disease process. There are further limitations to the current approaches. First, an association with CYP2C19 genotype does not prove that the activity of the enzyme is the proximate cause, since genetic linkage disequilibria and chance associations are always possible. Second, association may be under- or over-represented due to the additional involvement of other enzymes in the activation/detoxification pathways (e.g. phase II enzymes). In such cases, simultaneous genotyping should be performed to improve the validity of the findings. Third, the sample size used in the studies is often small, but such studies normally require very large number of individuals in order to reveal any potential association, a need that can only be met by high throughput genetic testing for CYP2C19 alleles. Phenotypic tests are used in some of the studies; such tests do not discriminate whether reduced activity of a particular enzyme is due to the disease itself or due to genetic polymorphism. This is particularly important to consider with CYP2C19, where its activity appears susceptible to the health of the patient. For such studies, genetic testing alone or in combination with phenotyping is the most appropriate.

## 4. Conclusions

Many drugs are metabolised by CYP2C19. The contribution of CYP2C19 to the metabolism of more than 25 drugs have been evaluated in individuals phenotyped and/or genotyped as CYP2C19 PM or EMs (see table IV and review).[19] For some drugs the pharmacokinetic differences between EMs and PMs of CYP2C19 are marked. On the basis of percentage change of oral clearance, the contribution of CYP2C19 may be categorised as high [80 to 100%; examples are (*R*)-hexobarbital, omeprazole, lansoprazole, pantoprazole, (*R*)-mephobarbital, carisoprodol and (*S*)-mephenytoin], medium (30 to 65%; examples are diazepam, flunitrazepam, moclobemide, *N*-desmethyldiazepam, clomipramine, trimipramine, imipramine, proguanil, fluoxetine, sertraline and citalopram) and low [<30%; examples are propranolol, phenytoin and (*R*)-warfarin].[19,148-150,329] Additionally, concurrently administered drugs can modulate CYP2C19 activity and thus contribute to the interindividual pharmacokinetic variability of CYP2C19 substrate drugs. A number of drugs (e.g. ticlopidine, fluoxetine, omeprazole and isoniazid) can inhibit the metabolism of CYP2C19 substrates, whereas rifampicin and artemisinin (but not phenobarbital and carbamazepine) have been so far identified as inducers. The activity of CYP2C19 appears to be diminished during liver cirrhosis and advanced age.

The critical question is: do the pharmacokinetic differences that result from genetic polymorphism or other factors matter in terms of the safety and efficacy of CYP2C19 substrates? The answer from this review is yes and no.

Most substrates, including the PPIs, have a wide therapeutic range and even the 5- to 10-fold difference in AUC between PMs and EMs is unlikely to influence the safety of these drugs. Although sedation from (*S*)-mephenytoin, hexobarbital and mephobarbital has been well documented in PMs of CYP2C19, these drugs are now rarely clinically used. A reduced dosage requirement for diazepam has been noted in Chinese patients as compared with Caucasians, but there are no controlled studies to confirm this claim. Reduced CYP2C19 activity is likely to increase the risk of adverse effects of antidepressants, most notably those adverse reactions produced by the TCAs, as these drugs have a narrow therapeutic range. This effect is particularly valid when other factors such as the activity of CYP2D6 are taken into account. The role of CYP2C19 in phenytoin metabolism is minor, but because of the narrow therapeutic range of the drug, the role of CYP2C19 in phenytoin toxicity appears important and physicians should monitor patients. It seems now apparent that, for example, the well-documented ticlopidine-phenytoin and isoniazid-phenytoin clinical interactions are mediated through inhibition of CYP2C19-mediated metabolism of phenytoin by these drugs. Physicians should be cautious when phenytoin is prescribed with CYP2C19 inhibitors. Because successful control of epilepsy requires phenytoin use for years, it may also be advisable to genotype patients, not only for CYP2C9 variants but also for CYP2C19 before initiation of phenytoin therapy.

Many patients, particularly the elderly and those with more severe health problems, often receive multiple drugs. In PMs, drugs may undergo significant shunting through less common pathways. Although this may not be a problem in healthy volunteers, it may have substantial relevance in patients who are ill when other pathways are simultaneously inhibited or induced by comedications or due to genetic polymorphism of the enzyme that catalyses the alternative pathway.

The recent demonstration of a significant association between CYP2C19 genetic polymorphism and the effective treatment of *H. pylori* infection and healing of peptic and duodenal ulcers by omeprazole and amoxicillin has opened an important avenue to use genotyping of CYP2C19 to predict the therapeutic response to omeprazole. Subsequent studies have essentially shown similar findings with other PPIs. Should a routine genotyping test be available to physicians to help them personalise and optimise therapy? If so, who should be genotyped? Is genetic testing cost-effective? What would be the risks associated with it? Up to now,

genetic testing of drug metabolising enzymes has been of little relevance to the practising physician and to patients. However, the use of this information to personalise drug therapy is emerging (e.g. CYP2D6). We believe that genotyping, particularly in Asian or other ethnic groups in which PMs of CYP2C19 are relatively common, is an important tool for predicting the effectiveness of omeprazole and related drugs. It appears cost effective (with little harm) to perform genotyping tests, even with current conventional tests. It is also our hope that, in the future, high throughput genetic testing will be developed to further reduce the cost of these tests.

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