Clinical relevance of genetic polymorphisms in the human CYP2C subfamily

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The human CYP2Cs are an important subfamily of P450 enzymes that metabolize approximately 20% of clinically used drugs. There are four members of the subfamily, CYP2C8, CYP2C9, CYP2C19, and CYP2C18. Of these CYP2C8, CYP2C9, and CYP2C19 are of clinical importance. The CYP2Cs also metabolize some endogenous compounds such as arachidonic acid. Each member of this subfamily has been found to be genetically polymorphic. The most well-known of these polymorphisms is in CYP2C19. Poor metabolizers (PMs) of CYP2C19 represent approximately 3–5% of Caucasians, a similar percentage of African-Americans and 12–100% of Asian groups. The polymorphism affects metabolism of the anticonvulsant agent mephenytoin, proton pump inhibitors such as omeprazole, the anxiolytic agent diazepam, certain antidepressants, and the antimalarial drug proguanil. Toxic effects can occur in PMs exposed to diazepam, and the efficacy of some proton pump inhibitors may be greater in PMs than EMs at low doses of these drugs. A number of mutant alleles exist that can be detected by genetic testing. CYP2C9 metabolizes a wide variety of drugs including the anticoagulant warfarin, antidiabetic agents such as tolbutamide, anticonvulsants such as phenytoin, and nonsteroidal anti-inflammatory drugs. The incidence of functional polymorphisms is much lower, estimated to be 1/250 in Caucasians and lower in Asians. However, the clinical consequences of these rarer polymorphisms can be severe. Severe and life-threatening bleeding episodes have been reported in CYP2C9 PMs exposed to warfarin. Phenytoin has been reported to cause severe toxicity in PMs. New polymorphisms have been discovered in CYP2C8, which metabolizes taxol (paclitaxel). Genetic testing is available for all of the known CYP2C variant alleles.

Keywords: CYP2C, CYP2C9, CYP2C19, mephenytoin, omeprazole, phenytoin, polymorphisms, tolbutamide, warfarin

Introduction

The purpose of this report is to review the clinical impact of polymorphisms of the CYP2C subfamily. The CYP2C subfamily consists of four members in humans (CYP2C8, CYP2C9, CYP2C18, CYP2C19). All members of this subfamily exhibit genetic polymorphisms. Genetic polymorphisms of CYP2C9 and CYP2C19 have been shown to have clinical consequences resulting in toxicity of some drugs in the affected individual, and may alter efficacy of

other drugs. Historically, the first polymorphism discovered in the CYP2Cs subfamily, was the well-known polymorphism in the metabolism of the anticonvulsant drug mephenytoin which was discovered in the 1980s [1]. Mephenytoin exists as two optically active enantiomers (the *R*- and *S*-enantiomers). The *S*-enantiomer is much more rapidly 4'-hydroxylated than the *R*-enantiomer and it is this pathway which is polymorphic. Population studies have shown that individuals can be categorized as extensive (EMs) or poor metabolizers (PMs) of this drug [2]. The PM trait is inherited as an autosomal recessive trait. PMs represent only 3–5% of Caucasians, but from 12–23% of most Asian populations. The PM phenotype is even more common throughout Polynesia and Micronesia [3] with a very high incidence (38–79%)

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in certain Vanuatu islands in eastern Melanesia. This polymorphism has been shown to be due to genetic polymorphisms in *CYP2C19*. The most predominant polymorphisms are two null alleles, one exhibiting a splice mutation in exon 5 and the second containing a premature stop codon in exon 4 [4, 5]. At least seven different inactivating mutations in *CYP2C19* have been described (Figure 1). These alleles include null mutations which prevent expression of the protein, as well as amino acid changes that affect catalytic activity of the protein [6–9]. Rare defective alleles have also been described for *CYP2C9* [10, 11]. Despite their low incidence, these polymorphic alleles are important because *CYP2C9* metabolizes many clinically important drugs. Polymorphisms in *CYP2C9* have the potential to affect the toxicity of *CYP2C9* drugs with somewhat lower therapeutic indices such as warfarin, phenytoin, and certain antidiabetic drugs. Genetic tests have been described for all known *CYP2C9* and *CYP2C19* alleles. Table 1 shows a list of drugs for which significant interactions have been demonstrated in individuals who have polymorphisms in *CYP2C* enzymes. Recently two new polymorphisms have been described in *CYP2C8* [12] which metabolizes taxol and other drugs [13]. The consequences of these polymorphisms have not been examined clinically.

Polymorphisms of *CYP2C18* have also been described [14, 15], but *CYP2C18* protein has not yet been found in detectable amounts in any tissues. Until this protein is shown to have some function *in vivo*, the polymorphisms in this enzyme are primarily of intellectual interest.

CYP2C19

CYP2C19 has been shown to metabolize not only *S*-mephenytoin but also diverse pharmacologically important therapeutic agents including the antiulcer drug omeprazole and other important proton pump inhibitors [16], certain tricyclic antidepressants such as imipramine [17–20] some barbiturates [1, 21]. It is also partially responsible for the metabolism of certain β -adrenoceptor blockers such as propranolol [22]. The biotransformation of the antimalarial drug proguanil to its active metabolite cycloguanil is partially dependent on *CYP2C19* [23].

Omeprazole is a proton pump blocker which acts on the H^+ / K^+ adenosine triphosphatase in gastric mucosa [24]. This drug was the first proton pump inhibitor to be registered to treat duodenal ulcers, peptic ulcers, reflux oesophagitis and other hyperacidic conditions. However, a number of other proton pump inhibitors have been recently introduced for similar purposes [25–27]. They are

Figure 1 *CYP2C19* alleles [4–9, 63, 64]. The background of the wild-type *CYP2C19*1A* allele is indicated by dark shading while the clear background represents the wild-type *CYP2C19*1B* allele which differs by a noncoding change at bp 99 and an Ile331Val substitution. The two intermediate shaded alleles contain the amino acid difference but not the noncoding change at bp 99. The nomenclature is according to the Human Cytochrome P450 (CYP) allele nomenclature committee at <http://www.imm.ki.se/CYPalleles/>

Table 1 Effects of CYP2C polymorphisms on clinical consequences of drugs.

Enzyme	Drug	Interaction
CYP2C9	Warfarin	Prolonged bleeding time, increased incidence of severe bleeding episodes in PMs [61]
	Glipizide, tolbutamide	Possibility of low blood sugar levels in PMs [54]
	Phenyoin	Signs of overdose: ataxia, disturbances of consciousness, mental confusion [55]
CYP2C19	Diazepam	Unacceptable prolonged sedation in PMs, unconsciousness noted more frequently in Asian populations [29]
	Omeprazole	Reports of decreases in cure rates at low dosage in homozygous or heterozygous EMs [31]

often used in combination with antibacterial treatments to eradicate *H. pylori* infections, which are closely associated with this disease. The 5-hydroxylation of omeprazole is metabolized by CYP2C19 [28], and omeprazole metabolism segregates with the metabolism of S-mephenytoin [16, 29]. After administration of omeprazole, the area under the plasma concentration *vs* time curves (AUC) is much higher in PMs of mephenytoin than EMs, and there is approximately a 10-fold difference in the oral clearance of omeprazole in PMs of mephenytoin due to impaired 5-hydroxylation. Individuals who are PMs of mephenytoin also have higher serum omeprazole/5-hydroxyomeprazole ratios than EMs [30]. Most PMs of omeprazole have been found to be homozygous for known PM alleles of CYP2C19. Recently, studies suggested that the CYP2C19 genotype may affect the cure rates for *H. pylori* infection in peptic ulcer patients. In one study, Japanese patients with peptic or duodenal ulcers received dual therapy with a low dose of omeprazole (20 mg day⁻¹ for 6–8 weeks) and amoxicillin (2000 mg day⁻¹ for 2 weeks) [31]. The cure rate for gastric ulcers and duodenal ulcers was 100% in CYP2C19PMs, 60% for heterozygotes containing one mutant allele and only 29% in individuals who were homozygous for the wild-type CYP2C19*1 allele. The high cure rate in CYP2C19PMs was suggested to be the consequence of markedly higher plasma concentration time curves of omeprazole in the PM phenotype. After omeprazole administration, gastric pH was highest in CYP2C19PMs, lowest in homozygous EMs, and intermediate in heterozygous EMs [32]. Amoxicillin is unstable and its antibacterial activity is higher at high pH. Gastrin levels were also higher in CYP2C19PMs than EMs. Omeprazole has also been reported to have anti-helicobacter activity [33]. However, the authors used a low dose of omeprazole in these studies, and the difference in cure rate would probably not have been observed at a higher dose.

There are several other proton pump inhibitors including pantoprazole, rabeprazole (E3810) [34] and lansoprazole whose metabolism has also been shown to be dependent on CYP2C19. For example, pantoprazole has a 6-fold increase in its plasma AUC, and a 5-fold

shorter half-life in EMs of mephenytoin than in PMs [26]. Pantoprazole lacks the 5-methyl group on the pyridine ring of omeprazole which is hydroxylated by CYP2C19. However, the demethylation of the 4-position of the pyridine ring is affected in CYP2C19PMs. Lansoprazole is structurally related to omeprazole and its 5-hydroxylation is mediated by CYP2C19. The oral clearance of lansoprazole was about 6.5 times lower in PMs of mephenytoin than EMs, and the AUC was also greater [25]. These data indicate that metabolism of lansoprazole, like that of omeprazole, is highly dependent on the CYP2C19 genotype.

A recent review [27] cited studies showing that individual variability in plasma concentrations of various proton pump inhibitors can be accounted for by genetically determined expression of CYP2C19 as determined by S-mephenytoin 4'-hydroxylation status. However, the magnitude of the contribution of CYP2C19 to metabolism of these proton pump inhibitors differed. The ratios of the AUC values in PMs *vs* EMs for omeprazole, pantoprazole, lansoprazole and rabeprazole were 6.3, 6.0, 4.7, and 1.8, respectively [35]. The metabolism of rabeprazole, which reacts nonenzymatically to produce a major metabolite, is less dependent on CYP2C19 status than other proton pump inhibitors. All these data suggest CYP2C19 genetic status could contribute to some interindividual variability in responsiveness to proton pump inhibitors particularly at low doses.

Proguanil is an antimalarial drug which is used for prophylaxis [36]. CYP2C19 has been proposed to be the principal enzyme involved in cycloguanil formation using inhibitor studies *in vivo* as well as *in vitro* [35]. However, CYP3A4, CYP1A2, and CYP2C19 have all been proposed to activate proguanil to its active metabolite cycloguanil [37, 38]. CYP2C19 and CYP3A4 accounted for ~73% and 16% of the conversion of proguanil to cycloguanil in human liver microsomes. Several studies have shown that the formation of cycloguanil cosegregates with PMs of mephenytoin, and the proguanil/cycloguanil ratio tends to be higher but the demarcation of the antimode is not clear [36, 38–41]. Therefore, the proguanil/cycloguanil ratio is not a good probe for the CYP2C19 polymorphism. An early study

showed a significant correlation of mephenytoin S/R ratios and chloroguanide/cycloguanil ratios and suggested a correlation between breakthrough parasitaemia episodes and the chloroguanide/cycloguanil ratio [42]. In a later study, the antimalarial efficacy in 62 individuals genotyped as CYP2C19 PMs was reported to similar to that of 33 patients with an EM genotype [3]. These authors suggested that the parent compound has intrinsic efficacy against the parasite and that metabolism is not necessary for activation. Since cycloguanil was seen in all subjects in the earlier study, another plausible explanation of the results of the later study might be the fact that other P450s such as CYP3A4 and CYP1A2 contribute to formation of the metabolite. Therefore, the clinical implications of CYP2C19 genotype on clinical efficacy of proguanil are uncertain.

A number of drugs are partially metabolized by CYP2C19. Diazepam, an anxiolytic drug is demethylated by CYP2C19. Plasma half-lives of diazepam were dramatically longer in individuals genotyped as homozygous for the defective CYP2C19*2 allele (84 h) than in individuals who were homozygous for the wild-type CYP2C19*1 allele (20 h), or individuals heterozygous for one defective CYP2C19 allele (64 h) [43, 44]. The half-life of the metabolite desmethyldiazepam was also longer in homozygous CYP2C19PMs. Asian populations in general have been reported to have slower metabolism of diazepam than Caucasians, which is attributed to the high frequency of the mutant CYP2C19*2 and CYP2C19*3 alleles in Asians [29]. Toxic doses of diazepam may occur as the result of this slower metabolism in PMs. As a consequence, more care must be taken with the dosage of diazepam in Asian individuals. The side-chain oxidation of propranolol is also metabolized partly by CYP2C19 [22], but only a small correlation between mephenytoin metabolism and side chain oxidation was observed *in vivo* [45]. This presumably reflects the fact that side chain cleavage is also carried out by CYP1A2, and ring hydroxylation by CYP2D6.

CYP2C19 also metabolizes the HIV protease inhibitor nelfinavir to its major circulating metabolite. However,

the metabolite has an antiviral activity similar to that of nelfinavir itself [46, 47]. As a consequence, the polymorphism does not appear to have a clinical effect on drug toleration or antiviral response to nelfinavir.

CYP2C9

CYP2C9 is the principal CYP2C in human liver [28]. It metabolizes many clinically important drugs including the diabetic agent tolbutamide, the anticonvulsant phenytoin, the S-enantiomer of the anticoagulant warfarin, Δ^1 -tetrahydrocannabinol and numerous anti-inflammatory drugs such as ibuprofen, diclofenac, piroxicam, tenoxicam, mefenamic acid [28], the antihypertensive losartan [48], and several new drugs including the antidiabetic drug glipizide and the diuretic torasemide [49, 50]. A rare polymorphism was reported in the metabolism of tolbutamide and phenytoin as early as the 1970s [51, 52]. Subsequently, the tolbutamide polymorphism was shown to be due a rare allele, CYP2C9*3, which carries an Ile359Leu mutation [10]. The same defect was identified in two individuals who were homozygous PMs of losartan. One of these was phenotyped for tolbutamide and was shown to be a PM for this drug. Another individual who was homozygous for the CYP2C9*3 allele was found to have diminished clearance of S-warfarin and an exacerbated response to warfarin [53]. In addition, a PM metabolizer of phenytoin, glipizide and tolbutamide was found to be homozygous for the CYP2C9*3 allele [54]. Clinical problems with toxicity and dosage adjustment of both warfarin and phenytoin have been found in CYP2C9 PMs [53, 55]. This allele has a frequency of approximately 6% in Caucasians (the frequency of homozygous CYP2C9*3 PMs is ~0.3%) [10]. The frequency in Asians is probably fairly similar. CYP2C19 also metabolizes phenytoin to a lesser extent and metabolism of phenytoin in CYP2C19 PMs has been reported to be slightly lower than that of EMs [56]. However, CYP2C9 probably accounts for 80–90% of the metabolism of phenytoin and therefore polymorphisms in CYP2C9 have a larger affect on clinical toxicity of the drug (Figure 2).

†substrate dependent

Figure 2 CYP2C9 alleles [10, 65, 66].

Recombinant CYP2C9*3 has a higher K_m for tolbutamide and S-warfarin 7-hydroxylation, torasemide metabolism, diclofenac 4'-hydroxylation, and a lower V_{max} for piroxicam 5'-hydroxylation, tenoxicam 5'-hydroxylation, mefenamic acid 3'-hydroxylation [10, 50, 57]. These changes resulted in lower intrinsic clearance values for all of the CYP2C9 substrates studied to date. In some cases, the effect appears to be the result of altered affinity of the enzyme for the substrate and in other cases, the mutation affects the V_{max} . Although the effects of the CYP2C9 polymorphisms on metabolism of these anti-inflammatory drugs have not been studied *in vivo*, the *in vitro* results suggest the possibility that individuals who are homozygous for CYP2C9*3 could have slower metabolism of these drugs. Since therapeutic indices of these drugs are relatively high, these polymorphisms would be less likely to have clinical consequences.

A second mutant allele of CYP2C9 (CYP2C9*2 containing an Arg144Cys substitution) has been reported to have decreased catalytic activity *in vitro* toward some substrates including warfarin but may have less effect on catalytic activity toward other substrates such as tolbutamide [10, 11]. The effect on catalytic activity *in vitro* appears to be dependent on the recombinant system used and has been attributed to an impaired ability of CYP2C9*2 to associate with reductase [58]. CYP2C9*2 has a frequency of approximately 8% in Caucasians but has a lower frequency in African-Americans and appears to be virtually absent in Asians [10]. A recent preliminary study indicated that phenytoin metabolism was affected in a compound heterozygote (CYP2C9*2/CYP2C9*3) and a CYP2C9*2 homozygote although the details of this study are not yet available [59]. An earlier study [60] reported a slightly higher incidence of the CYP2C*2 allele in individuals who required a lower dose of warfarin for maintenance for anticoagulative therapy. A later study [61] reported a higher incidence of variant CYP2C9 alleles (CYP2C9*2 and CYP2C9*3) in individuals requiring a low dose of warfarin to maintain optimum anticoagulation than in those who required a high dose. The incidence of serious and life-threatening bleeding episodes was four times higher in the group of patients requiring a low dose of warfarin. There was also increased difficulty in establishing optimum coagulation in this group with delayed discharges from an anticoagulant clinic, multiple visits to the clinic, and additional studies to explain unusual warfarin sensitivity. Unfortunately, the PCR primers used in the genetic tests in the latter two studies were not specific for CYP2C9, but have been shown to amplify CYP2C19 [62]. Since CYP2C19, like wild-type CYP2C9, contains an Arg144 and Ile359, results of these studies may in fact under represent the incidence of the PM allele. Despite these problems, the latter study is consistent with serious

effects of the polymorphic CYP2C9 alleles on coagulation times after administration of warfarin.

CYP2C8

CYP2C8 metabolizes the anticancer drug paclitaxel [13]. A recent preliminary report from our laboratory has shown that CYP2C8 is also polymorphic [12]. One of the polymorphic alleles is defective in metabolizing paclitaxel *in vitro*. Future studies will address whether this polymorphism has clinical consequences on the CYP2C8 substrates such as paclitaxel *in vivo*.

Conclusions

Drugs for which CYP2C polymorphisms have been reported to impact clinical effects are documented in Table 1. CYP2C9 has been shown to metabolize many clinically used drugs. Polymorphisms in this enzyme seriously affect the toxicity of drugs such as the anti-convulsant phenytoin, and the common anticoagulant warfarin. The polymorphism in CYP2C19 has been shown to markedly affect the half-life of the common anxiolytic drug diazepam, with a the result that a much lower dose is required in many Asians. Individuals homozygous for the CYP2C19 polymorphism have a markedly longer half-life of the antiulcer drug omeprazole with increased efficacy at low doses of the drug. These polymorphisms continue to be studied with respect to their effects on toxicity and efficacy of clinically used drugs. The varied incidence of these alleles results in variations in risk and efficacy in different racial populations. New polymorphisms in CYP2C8 are of potential interest in future clinical studies.

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