Clinical relevance of genetic polymorphisms in the human CYP2C9 gene

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Abstract

Cytochrome P450 (CYP) 2C9 hydroxylates about 16% of drugs in current clinical use. Of special interest are those with a narrow therapeutic index, such as S-warfarin, tolbutamide and phenytoin, where impairment in CYP2C9 metabolic activity might cause difficulties in dose adjustment as well as toxicity. Single-nucleotide polymorphisms (SNP) in the CYP2C9 gene have increasingly been recognized as determinants of the metabolic phenotype that underlies interindividual and ethnic differences. Apart from the wild-type protein CYP2C9*1 at least five allelic variants produce allozymes with reduced or deficient metabolic activity. Among white populations only CYP2C9*2 and CYP2C9*3 variants are of significance, with allelic frequencies of 0.08–0.14 and 0.04–0.16, respectively. In contrast, in Africans (African-Americans and Ethiopians) and Asians both variants are much less frequent (0.005–0.04), and CYP2C9*4 has not yet been detected in Asians. CYP2C9*4 has been exclusively identified in Japanese patients, and CYP2C9*5 and *6 were only found among African-Americans with a low allelic frequency of 0.017 and 0.006, respectively. Furthermore in Japanese a CYP2C9 promotor variant of four linked SNPs was correlated with reduced intrinsic clearance of phenytoin in vitro. Subjects who are carriers of one or more variant alleles may be at risk for adverse drug reactions/toxicities when prescribed drugs extensively metabolized by CYP2C9.

Keywords CYP2C9, polymorphisms, warfarin, diclofenac, 5′-flanking region.

Introduction

Genetically determined differences in drug-metabolizing enzyme activity can lead to a wide interindividual variability in drug response, resulting in altered efficacy or toxicity in the affected individuals [1]. For example, single-nucleotide polymorphisms in the cytochrome P450 (CYP) 2C9 gene produce differences in the metabolism of certain drug substrates that have increasingly been recognized to have clinically significant consequences.

CYP2C9 appears to be the major CYP2C isoform found in the human liver [2–4]. It is one of four known members of the CYP2C subfamily [5], including the CYP isoforms CYP2C8, CYP2C18 and CYP2C19, that share > 82% of amino acid identity [2]. Despite the high sequence similarity, the human CYP2C isoforms exhibit relatively little overlap of substrate specificity [2,4].

CYP2C9 hydroxylates a wide array of mostly acidic substrates in diverse therapeutic categories, about 16% of drugs in current clinical use, including the antidiabetic agents tolbutamide, glibenclamide, glimepiride and glidezide, the anticonvulsant phenytoin, the active S-enantiomer of the anticoagulants warfarin, acenocoumarol and phenprocoumon, the antihypertensive drugs losartan and irbesartan, the diuretic torasemide and numerous nonsteroidal anti-inflammatory drugs such as ibuprofen, diclofenac, piroxicam, tenoxicam, mafenamic acid and celecoxib [2,6–14]. Of special interest are drugs with a narrow therapeutic index, such as S-warfarin, tolbutamide and phenytoin, because impairment in CYP2C9 metabolic activity might cause difficulties in dose adjustment as well as toxicity [15,16].

CYP2C9 gene structure and allelic variants

The CYP2C9 gene consists of nine exons encoding a protein of 490 amino acids [2]. Allelic variants are caused by single nucleotide exchanges leading to nonsynonymous amino acid substitutions, differing at only a few residues in the coding region. In addition to the wild-type protein CYP2C9*1 (Arg144, Ile359, Asp360), four allelic variants are known to produce allozymes with reduced intrinsic metabolic activity (see Fig. 1): CYP2C9*2 (Cys144, Ile359, Asp360),...
CYP2C9*3 (Arg144, Leu359, Asp360), CYP2C9*4 (Arg144, Thr359, Asp360) and CYP2C9*5 (Arg144, Ile359, Glu360) [17–21]. More recently a single basepair deletion polymorphism CYP2C9*6 (818delA) resulting in inactive CYP2C9 protein has been described [22]. An excellent review on their location, has recently been published [13].

Sequencing studies indicate that only CYP2C9*2 and CYP2C9*3 variants are of particular importance among white populations, where the allelic frequencies are in the range of 0.08–0.14 and 0.04–0.16, respectively, and about 0.5%–2.5% of such individuals are homozygous for the CYP2C9*2 and *3 allele or heterozygous for the CYP2C9*2/*3 allele [21,23–28]. In contrast, in Africans (African-Americans and Ethiopians) and Asians both variants are much less frequent (0.005–0.04), and Americans and Ethiopians) and Asians both variants are much less frequent (0.005–0.04), and CYP2C9*2 has not been detected yet in Asians [21,24,26,29,30]. Another new variant, CYP2C9*4, has been exclusively identified in Japanese epileptic patients [31], and the recently discovered novel allele CYP2C9*5 was only found among African-Americans with a low allelic frequency of 0.017 [21]. CYP2C9*6 was also only detected in African-Americans with an allelic frequency of 0.006. The results of population prevalence according to ethnicity of the CYP2C9 genotype including the *2, *3 and *5 alleles from the largest genotyping studies are summarized in Table 1.

In addition, genetic polymorphisms have been identified in the 5′-flanking region of CYP2C9 in Japanese individuals. Two different haplotypes, TCGG (wild-type) and CGAA (variant allele), were observed. The allelic pattern of the four linked single-nucleotide polymorphisms (Pattern 2: T1912C, C1886G, G1538A, G982A) was associated with a reduced intrinsic clearance in vitro compared with wild-type pattern 1 without those mutations [32]. Interestingly, the promotor variant CGAA was strongly associated with the CYP2C9*3 allele in exon 7, and this linkage has been finally shown to be the most important haplotype determining the CYP2C9 metabolic capacity among the six observed sequence patterns of the 5′-flanking region.

### Table 1: Population distribution of CYP2C9 genetic polymorphisms (*2, *3 and *5 allele) according to ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>*1/*2</th>
<th>*1/*3</th>
<th>*2/*2</th>
<th>*2/*3</th>
<th>*3/*3</th>
<th>*1/*5</th>
<th>n</th>
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<td>2.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>140</td>
<td>Dickmann et al. [21]</td>
</tr>
<tr>
<td>British</td>
<td>19.1</td>
<td>9.4</td>
<td>0.5</td>
<td>1.1</td>
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<td>–</td>
<td>561</td>
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</tr>
<tr>
<td>Israeli</td>
<td>19.0</td>
<td>15.0</td>
<td>3.0</td>
<td>0</td>
<td>1</td>
<td>–</td>
<td>100</td>
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</tr>
<tr>
<td>Italian</td>
<td>15.3</td>
<td>14.0</td>
<td>2.5</td>
<td>1.9</td>
<td>1.3</td>
<td>–</td>
<td>156</td>
<td>Loebstein et al. [28]</td>
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<tr>
<td>Spanish</td>
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<td>23.5</td>
<td>1.9</td>
<td>8.9</td>
<td>0</td>
<td>–</td>
<td>157</td>
<td>Scordo et al. [26]</td>
</tr>
<tr>
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<td>11.6</td>
<td>0.5</td>
<td>1.9</td>
<td>0.7</td>
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<td>2.5</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
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<td>98</td>
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</tr>
<tr>
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<td>4.1</td>
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<td>0</td>
<td>0</td>
<td>–</td>
<td>100</td>
<td>Sullivan-Klose et al. [24]</td>
</tr>
<tr>
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<td>3.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>115</td>
<td>Nasu et al. [30]</td>
</tr>
<tr>
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<td>0</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>574</td>
<td>Wang et al. [29]</td>
</tr>
</tbody>
</table>

* Polymorphism not investigated.

Population prevalence of CYP2C9 genotype as a percentage of total individuals analysed in the study (n).
enzyme [34]. Moreover, the first crystallographic structure shown for a mammalian P450 2C5 provides a concordant structural basis for the observed effects of mutations within those predicted SRS regions on enzyme activity in the CYP2 family [35].

In a recent study, recombinant CYP2C9*3 exhibited a reduced intrinsic clearance ($V_{\text{max}}/K_m$) for the seven studied CYP2C9 substrates compared with the wild-type enzyme [36]. A higher $K_m$ value without a change of the $V_{\text{max}}$ values was found for tolbutamide methylhydroxylation, S-warfarin hydroxylation, torasemide metabolism and diclofenac 4’ hydroxylation, whereas for the hydroxylation of piroxicam, tenoxicam and mefenamic acid only lower $V_{\text{max}}$ values were revealed. A similar observation was made for the CYP2C9*5 polymorphism using a baculovirus expression system, where a 6-fold to 31-fold lower intrinsic clearance for the hydroxylation of diclofenac and S-warfarin was observed, respectively, mainly through an increase of $K_m$ values [21]. However, the CYP2C9*3-mediated intrinsic clearance reduction for S-warfarin hydroxylation was associated with both an increase in $K_m$ and a decrease in $V_{\text{max}}$. Thus, the effect caused by expression of the different CYP2C9 variants appears to be the result of either altered affinity of the enzyme for the substrate and/or an affected $V_{\text{max}}$ with a variable magnitude in impairment of oxidative metabolism that may be substrate dependent. Finally, differences among allozymes of any CYP isoform may variably contribute to the recognition and binding of discrete classes of substrates [37].

**Drug substrates of CYP2C9**

**Oral anticoagulants**

**Warfarin**

More than 80% of the pharmacologically more active S-enantiomer of warfarin is eliminated by CYP catalysed biotransformation to 6- and 7-hydroxy S-warfarin, whereas CYP2C9 is the main cytochrome P450 responsible for the 6- and 7-hydroxylation pathways [38–40]. Thus, the responsible enzyme activity regulates the steady-state plasma concentration of S-warfarin and becomes a critical factor in anticoagulant therapy [41–43].

Kinetic studies with the expressed CYP2C9 variants indicate a significant impairment of S-warfarin hydroxylase capacity: the allozymes CYP2C9*2 and CYP2C9*3 showed an approximately 5-fold and 25-fold lower intrinsic clearance ($V_{\text{max}}/K_m$) compared with the wild-type gene product, respectively [17,18]. The recently described CYP2C9*4 allele in Japanese epileptic patients has not been studied yet with respect to warfarin metabolism, but significantly reduced enzyme activity for diclofenac hydroxylation in vitro has been demonstrated [20]. The intrinsic clearance for the CYP2C9*5 allozyme found in African-Americans was shown to be 31-fold lower for 7-hydroxylation of S-warfarin compared with the wild-type [21].

*In vivo*, a homozygous individual for the CYP2C9*3 allele was found to have a reduction in clearance of S-warfarin and an exacerbated response to warfarin, thus the CYP2C9*3/*3 genotype was clearly shown to be linked to warfarin sensitivity [15]. A strong association has been demonstrated between the presence of one or more CYP2C9*2 and CYP2C9*3 variant alleles and low-dose requirements for warfarin in a large number of published studies, whereas in most cases the dose is lowest if CYP2C9*3 is present [28,44–46]. Moreover, the higher sensitivity for warfarin in two studies was correlated with a higher incidence of major bleeding complications [44,46]. A recent study also demonstrated a clear relationship between S-warfarin clearance and CYP2C9 genotype [47]. Therefore, there seems to be a reasonable correlation between the observed *in vitro* activities of these variant forms of CYP2C9 and the *in vivo* consequences for metabolic clearance of warfarin. In addition to the CYP2C9 genotype, age and environmental factors were also discussed to be a possible cause for a decline in warfarin daily dose [28]. However, all published studies to date have been retrospective, therefore prospective case-control and cohort studies with a large patient number may provide additional information on the value of CYP2C9 genotyping to warfarin treatment and safety.

**Aceclofenac and phenprocoumon**

The main alternatives to warfarin, the coumarinic derivatives aceclofenac and phenprocoumon, are widely used in certain European countries [12]. The chemical structure of these racemates is closely related to warfarin, and both S-Enantiomers are substrates of CYP2C9 [48,49]. Besides CYP2C19 and CYP1A2, a role of CYP2C9 has also been demonstrated for the more active R-acenocoumarol [48]. In the case of acenocoumarol there is increasing clinical evidence that the CYP2C9*3 allele only is related to a low-dose requirement for this drug, a higher frequency of over-anticoagulation and an unstable anticoagulant response [50–52], and even one copy of CYP2C9*3 might profoundly reduce the oral drug clearance [53]. In the case of phenprocoumon no relationship of dosage and CYP2C9 genotype has been established yet. A more complex situation needs to be assumed because it is a potent inhibitor of its own metabolism [49].

Although there is accumulating evidence on the relationship between the CYP2C9 genotype and dose requirements, an individual’s anticoagulant dose will likely depend on a complex interaction between genetic and environmental factors. Genotyping for the more common CYP2C9 alleles may therefore be an aid to successful anticoagulation and the extent of clinical monitoring needed [12].

**Oral antidiabetics**

**Tolbutamide**

In humans tolbutamide is metabolized almost exclusively by methylhydroxylation that accounts for 85% of tolbutamide clearance; the initial and rate-limiting step [54,55]. There is evidence both *in vitro* and *in vivo* that CYP2C9 solely mediates the tolbutamide hydroxylation, and the antidiabetic
agent is therefore accepted widely as a prototypic substrate for the assessment of hepatic CYP2C9 activity [37,56].

A poor metabolizer phenotype in the metabolism of tolbutamide and a possible genetic regulation was first reported in 1979 [57]. Pharmacokinetics of tolbutamide in 50 nondiabetic subjects, including twins, showed an almost 9-fold variation of the elimination rate constant; the corresponding range of half-lives was 2-9-25-0 h. According to these data about 30% of the population was estimated to be a ‘poor metabolizer’; however, the true genotypes had not yet been defined. In a later in vivo study genotyping of an individual with a tolbutamide half-life of 37 h confirmed homozygosity for the rare CYP2C9*3 allele that carries the Ile359Leu mutation [58], and was subsequently identified to cause this phenotype [24,59]. The expressed recombinant CYP2C9*3 had been shown to exhibit lower intrinsic clearance (V_max/Km) for tolbutamide methylhydroxylation than did the wild-type, caused by a higher Km value without a change of the V_max values. It was proposed that the tolbutamide poor metabolizer status could be attributed to homozygosity for the CYP2C9*3 allele.

In a recent study the relationship between CYP2C9 genotype and tolbutamide plasma clearance (CL/F) phenotype in 23 healthy subjects expressing all six CYP2C9 allele combinations was reported [60]. Tolbutamide oral clearances were: 0-97 (1/1), 8-88 (1/2), 0-75 (2/2), 0-56 (1/3), 0-45 (2/3) and 0-16 (3/3) L h⁻¹. On the basis of this genotype-phenotype analysis the authors proposed a classification of tolbutamide extensive (CYP2C9 genotypes 1/1; 1/2; 2/2), intermediate (1/3; 2/3) and slow metabolizer (3/3) phenotypes. According to this classification, intermediate and slow metabolizers may be predicted to comprise approximately 12% and 1%, respectively. Consistent with these data are two recently published studies: In Korean subjects genotyped for CYP2C9 a 2-fold higher area under the concentration-time curve (AUC) of tolbutamide for CYP2C9*1/*3 heterozygotes compared with subjects homozygous for the wild-type allele was reported [61], and in 15 Caucasian subjects (CYP2C9*1 heterozygotes and wild-type subjects, each group n = 5) a 1-5-fold and 1-9-fold increase in tolbutamide AUC as well as a 29% and 48% reduction of tolbutamide clearance were revealed, respectively, in subjects expressing *1/*2 and *1/*3 genotypes vs. *1/*1 carriers [62]. However, the clinical consequences of CYP2C9 polymorphisms for the treatment with oral hypoglycaemic agents such as tolbutamide, remain unclear [63]. To evaluate the pharmacodynamic effect nondiabetic healthy subjects were monitored for blood/serum glucose (and plasma insulin [60]) following tolbutamide administration (500 mg, p.o.) with or without a challenge with glucose or dextrose in the three prospective studies mentioned above [60-62]. No relationship of glucose or insulin concentrations and CYP2C9 genotype was reported by Lee et al. and Kircheimer et al. [60,62], moreover, hypoglycaemia has not been observed, even without additional carbohydrate administration after tolbutamide. In contrast, in Koreans the enhancement in serum glucose increase relative to baseline was significantly lower in CYP2C9*1/*3 heterozygotes compared with homozygotes for the wild-type allele [61]. Further data are necessary to support the approach of dosage adjustment on the basis of genotype in diabetic patients, and pharmacodynamic monitoring remains the rational option for tolbutamide treatment [63].

**Glibenclamide and glimepiride**

Genetic polymorphisms of CYP2C9 affected pharmacokinetics of the two sulfonylurea antidiabetic drugs glibenclamide and glimepiride in healthy volunteers [6,7]. In individuals heterozygous for the CYP2C9*3 allele the glibenclamide AUC was 280% higher [7], and in CYP2C9*3 homozygotes the oral clearance was reduced by more than 50% in relation to the wild-type carriers [6]. Furthermore, in heterozygotes for CYP2C9*3 the glimepiride AUC was also significantly increased by 267% of the respective values in subjects with the 1/*1 genotype [7]. In both studies blood glucose responses to glibenclamide and glimepiride were not significantly affected, whereas the insulin secretion after glibenclamide ingestion was higher in subjects with the 3/*3 genotype compared with the other genotypes [6].

**Anticonvulsants**

**Phenytoin**

The major pathway of phenytoin metabolism is 4’ hydroxylation, which accounts for approximately 80%-90% of the drug elimination and is mainly mediated by CYP2C9 according to in vivo and in vitro studies [64,65]. There is evidence that the CYP2C9 activity is rate-limiting in phenytoin metabolic clearance [37].

Site-directed mutagenesis revealed that phenytoin hydroxylase activity of CYP2C9*2 and *3 variants was lower compared with the wild-type enzyme [66]. In vivo, a modest decrease in the maximal rate of phenytoin elimination (~30%) was observed in six Japanese epileptic patients heterozygous for CYP2C9*3 compared with the 38 patients homozygous for the CYP2C9*1 allele [67]. Furthermore, pharmacokinetics of phenytoin in an individual homozygous for the CYP2C9*3 allele showed a more than 4-fold increase in AUC and a 21% decrease in phenytoin clearance compared with 24 healthy subjects genotyped as wild-type [10]. Genotyping data indicates that 4%-16% of Caucasians are heterozygous and less than 1% homozygous for the CYP2C9*3 allele [24], in agreement with the estimated frequencies of phenytoin and tolbutamide poor metabolizer phenotypes [68,69]. Nonetheless, because phenytoin is metabolized almost exclusively by CYP2C9, this rare polymorphism can lead to toxicity and difficult dosage adjustment of phenytoin in the affected individuals. Indeed, in a recent case report concerning a heterozygous CYP2C9*3 allele carrier, excessive phenytoin concentrations were described despite the modest daily dose taken, leading to signs of central nervous system intoxication [16]. Furthermore, a strong association between CYP2C9 genotype and phenytoin maintenance dose requirement was shown in 60 epileptic patients on long-term phenytoin

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therapy [70]. Those patients, having at least one variant CYP2C9 allele *2 and *3, required a significant lower dose of phenytoin than wild-type individuals to reach an effective serum concentration; there were no patients homozygous for the CYP2C9*3 allele present in this study. Finally, the recently identified loss of function mutation in CYP2C9 (*6) was associated with a marked increase in half-life and clinical toxicity to phenytoin in a subject homozygous for this polymorphism [22]. Since phenytoin has a narrow therapeutic index, dosage adjustment based on CYP2C9 genotype, especially at the beginning of therapy, would be of value in order to lower the risk of concentration-dependent drug intoxications in variant carriers.

Nonsteroidal anti-inflammatory drugs

Diclofenac and ibuprofen

Diclofenac 4′-hydroxylation is mainly mediated by CYP2C9 in vitro [71]. The in vitro effects of CYP2C9 variant alleles on the extent of the reduction in 4′-hydroxylation were less pronounced than those observed with other CYP2C9 substrates such as warfarin, tolbutamide and phenytoin [36]. Moreover, the absence of clinically significant effects in the CYP2C9-mediated metabolism of diclofenac has been reported in several in vivo studies with a lack of pharmacokinetic as well as pharmacodynamic changes. A prospective evaluation of diclofenac pharmacokinetics in 12 subjects revealed no significant differences between CYP2C9*3 heterozygotes and wild-type subjects regarding any parameter after a single 50 mg oral diclofenac dose [72]. Three similar investigations in healthy volunteers with all combinations of the CYP2C9 variants *2 and *3 confirmed the lack of genotypic influence on diclofenac disposition [73–75]. In addition, Kirchheiner et al. also investigated the formation of thromboxane B2 and prostaglandin E2, reflecting constitutively expressed cyclooxygenase 1 (COX-1) and inducible cyclooxygenase 2 (COX-2) activity, respectively, as a surrogate parameter for pharmacodynamics of diclofenac [75]. Marked diclofenac-mediated inhibition of COX-1 and COX-2 activity was detected to be independent of CYP2C9 genotype.

The widely used nonsteroidal anti-inflammatory drug ibuprofen is another nonselective inhibitor of COX-1 and COX-2. In vitro data indicated that CYP2C9 might be the major S-ibuprofen hydroxylase, whereas R-ibuprofen appeared to be metabolized by CYP2C8 [71,76]. One recent study investigated the impact of CYP2C9 polymorphisms in 21 healthy volunteers on ibuprofen pharmacokinetics and inhibition of COX-1 and COX-2 following an oral dose of 600 mg ibuprofen [77]. S-ibuprofen oral clearance was associated with the CYP2C9*2 genotype: 3·25, 2·38 and 1·52 L h−1 in carriers of CYP2C9*1/*1, *1/*3 and *3/*3, respectively, whereas the CYP2C9 variant *2 had no significant effect. Moreover, in carriers of the CYP2C9*3 allele pharmacodynamics of ibuprofen measured as the inhibition of thromboxane B2 as well as prostaglandin E2, were strongly dependent on the genotype.

Celecoxib

Methyl hydroxylation of celecoxib, a novel COX-2 inhibitor, has been shown to be primarily catalyzed by human liver microsomal CYP2C9 in vitro (approximately 72%–92%), although CYP3A4 also plays a role (approximately 0%–27%) [14]. Benner et al. reported no association between the CYP2C9 variants *2 and *3 and the celecoxib steady-state disposition after 400 mg oral celecoxib daily for 15 days in 25 healthy subjects [74]. This lack of genotypic influence on celecoxib and diclofenac disposition in contrast to ibuprofen might demonstrate substrate-specific effects, which need further investigation.

Antihypertensive drugs

Losartan

The selective angiotensin II receptor antagonist losartan undergoes primarily CYP2C9-mediated oxidative metabolism to its active metabolite E3174 [78], whereas CYP3A4 also appears to have a limited role in this metabolic reaction. An identified losartan poor metabolizer converted less than 1% of the administered losartan dose to the active metabolite E3174, and genotyping subsequently revealed a subject with homozygous CYP2C9*3 allele [79]. This individual also demonstrated reduced metabolite levels of tolbutamide and phenytoin and a normal erythrocytic breath test, revealing functionally deficient CYP2C9 and normal CYP3A4 activity. These findings confirmed the predominant role of CYP2C9 in the conversion of losartan to E3174, moreover providing evidence regarding the potential clinical implications of the CYP2C9 polymorphisms in losartan metabolism. More recently, one study investigated the pharmacokinetics of losartan in relation to the CYP2C9 genotypes on healthy volunteers [9]. The authors report a 30-fold, 3-fold and 2-fold increase in the ratio of losartan AUC to the metabolite E3174 AUC in subjects with the CYP2C9*3/*3, *2/*3 and *1/*3 genotype, respectively. Furthermore, the CYP2C9*3 allele was shown to be associated with a decreased formation of the metabolite in plasma and urine. However, the influence of CYP2C9 genotypes on clinical use of losartan is not known yet.

Irbesartan

There is in vitro evidence that CYP2C9 also plays a major role in the metabolism of another selective angiotensin II receptor antagonist irbesartan [80,81]. In vivo effects of CYP2C9 polymorphisms on pharmacokinetics and the clinical use of irbesartan are currently under investigation [13]. In an in vivo study a diastolic blood pressure (DBP) response in 49 patients with essential hypertension given irbesartan for 12 weeks in relation to the CYP2C9 genotype was described: 7·5% and 14·4% reduction in DBP compared with baseline, respectively [82]. However, DBP in the three patients heterozygous for the *3 allele differed not markedly from baseline (approximately 1·8% difference).
Other substrates

Limited, preliminary data describing the potential effects of CYP2C9 genotype on the oxidative metabolism of other substrates in vivo have also been reported. After a single 10 mg glipizide dose, a single healthy subject homozygous for CYP2C9*3 was reported to have a 2-fold increase in half-life, a 5.5-fold reduction of oral clearance and a 5.5-fold increase in the AUC as well as profound symptoms of hypoglycaemia compared with 23 control individuals [10]. In addition to the data reported with tolbutamide, these findings suggest a potentially significant effect of the CYP2C9*3 variant on the pharmacokinetics and serious adverse event rate of oral hypoglycaemic drugs that are substrates of CYP2C9. For the diuretic torsemide, in vivo effects of the CYP2C9 genotype on pharmacokinetics and clinical use are not known yet but are currently under investigation.

Conclusion

CYP2C9 ranks among the most important drug metabolizing CYP isozymes present in the human liver. It hydroxylates a wide array of clinically used drugs. Modulation of CYP2C9 activity by genetic factors, stimulatory and inhibitory interactions and age effects, cause a wide interindividual variability for elimination and/or dosage requirement. Of special interest are compounds with a narrow therapeutic window, for example, selective cyclooxygenase-II inhibitors. Genetic polymorphisms, especially the homozygous appearance of the variant allele CYP2C9*3, can lead to a marked impairment in CYP2C9 metabolic activity in the affected individuals, and is likely to be associated with effects on efficacy, dosage adjustment and severe toxicity. Furthermore, differences in incidence of variant alleles among various ethnic populations may contribute to the outcome and risks to certain drug therapies.

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References


