Research article/Raziskovalni prispevek

GENETIC POLYMORPHISM OF CYTOCHROMES P450 2C9 AND 2C19 IN SLOVENIAN POPULATION

GENETSKI POLIMORFIZEM CITOKROMOV P450 2C9 IN 2C19 V SLOVENSKI POPULACIJI

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Abstract – Background. *Cytochrome P450 2C9 (CYP2C9) and 2C19 (CYP2C19) participate in metabolism of many clinically important drugs. Genetic polymorphisms of the CYP2C9 and CYP2C19 genes are described which may affect drug treatment. The aim of this study was to determine the frequencies of polymorphic CYP2C9 and CYP2C19 alleles in Slovenian population in order to estimate the proportion of the population that might experience adverse drug reaction.*

Methods. *The polymorphism of CYP2C9 and CYP2C19 was analysed by a genotyping technique, based on polymerase chain reaction (PCR) followed by restriction enzyme analysis. DNA samples from 129 unrelated healthy subjects were obtained from the Blood Transfusion Centre of Slovenia and University Children's Hospital in Ljubljana.*

Results. *In the analysed group of samples one-third of individuals carried at least one of the defective CYP2C9 alleles while among them 3.2% of individuals had both alleles affected. The frequencies of CYP2C9*2 and CYP2C9*3 were 0.122 and 0.063, respectively. Almost one-third of Slovenian individuals analysed carried at least one of the CYP2C19 polymorphic allele. The frequencies of CYP2C19*2 and CYP2C19*3 were 0.159 and 0.004, respectively.*

Conclusions. *The results of our study indicate that approximately one-third of the patients from Slovenian population may require either adjustments of dose or increased monitoring when initiating treatment with CYP2C9 and CYP2C19 substrates having a narrow therapeutic index. High risk of adverse drug reaction may be expected in 1–3% of eventual patients.*

Izvleček – Izhodišča. *Citokromi P450 2C9 (CYP2C9) in 2C19 (CYP2C19) so vključeni v presnovo različnih zdravil. Kodirata jih polimorfna gena CYP2C9 in CYP2C19, zaradi česar prihaja do interindividualnih razlik v hitrosti in učinkovitosti zdravljenja. Genetski polimorfizem postane klinično pomemben predvsem pri zdravilih, ki imajo majhno terapevtsko širino. Namen raziskave je bil določiti frekvence polimorfnih alelov CYP2C9 in CYP2C19 v slovenski populaciji in na ta način oceniti delež posameznikov s povečanim tveganjem za nastanek neželenih učinkov zdravila.*

Metode. *Polimorfizem genov CYP2C9 in CYP2C19 smo analizirali s tehniko genotipizacije. Ta temelji na pomnoževanju ustreznega dela genomske DNK z verižno reakcijo s polimerazo in na cepitvi pomnoženega odseka z ustreznim encimom. Uporabili smo vzorce DNK 129 nesorodnih, zdravih posameznikov, ki smo jih dobili na Centru za transfuzijo Republike Slovenije in na Pediatrični kliniki v Ljubljani.*

Rezultati. *V analizirani skupini smo zasledili, da je ena tretjina posameznikov imela vsaj enega od polimorfnih alelov CYP2C9, med njimi pa je bilo 3,2% posameznikov z obema polimorfnima aleloma. Frekvenci alelov CYP2C9*2 in CYP2C9*3 sta bili 0,122 oz. 0,063. Podobno je skoraj ena tretjina posameznikov imela vsaj enega od polimorfnih alelov CYP2C19. Frekvenci alelov CYP2C19*2 in CYP2C19*3 sta bili 0,159 oz. 0,004.*

Zaključki. *Rezultati naše raziskave kažejo, da ima približno tretjina Slovencev zmanjšano metabolno kapaciteto za zdravila, ki se presnavljajo prek CYP2C9 oz. CYP2C19. Takim osebam bi bilo treba med zdravljenjem z zdravili z majhno terapevtsko širino ustrezno prilagoditi odmerek zdravila oz. natančneje spremljati potek zdravljenja, še posebno v obdobju uvajanja zdravila. Pri 1–3% takšnih posameznikov pa je večja verjetnost pojava hujših neželenih učinkov zdravil.*

Introduction

Cytochromes P450 (CYPs) are a superfamily of heme proteins which catalyse many types of reactions, predominantly hydroxylations. They participate in oxidative metabolism of a wide variety of structurally diverse compounds, including endogenously synthesised compounds such as steroids and fatty acids, as well as exogenous compounds such as drugs, car-

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cinogens and environmental agents. Genes for cytochromes P450 *(CYPs)* are classified according to their sequence similarities, into distinct gene families (designated by *CYP* followed by an Arabic numeral) and subfamilies (designated by a letter following the Arabic numeral). Individual genes are designated by the second Arabic numeral following the letter (1).

CYP2C gene subfamily represents a cluster of four genes on the chromosome 10q24, arranged in the sequential order *CYP2C8-CYP2C9-CYP2C19-CYP2C18* (2). CYP 2C8, 2C9, 2C18 and 2C19 share more than 82% amino acid identity. Despite the high level of sequence similarity they exhibit relatively little overlap of substrate specificity (3). All members of this subfamily are genetically polymorphic. Among them and CYP2C19 are clinically the most important. They both participate in metabolism of many drugs with narrow therapeutic index and genetic polymorphism may result in increased toxicity or in altered efficacy of such drugs in the affected individual (4–7). Beside genetic polymorphism, the additional causes for variations in drug metabolism are: induction or inhibition of cytochromes P450 due to concomitant drug therapies or environmental factors, physiological status and accompanying disease (8). In respect to the metabolic capacity for certain drug, individuals can be phenotypically divided into two groups: extensive metabolizers (EMs) and poor metabolizers (PMs) (9).

Best known drug substrates for CYP2C9 are weak acids containing carboxylic group in their structure. Oral hypoglycemic agents such as tolbutamide, some antiepileptic drugs such as phenytoin, oral anticoagulant warfarin, a number of nonsteroidal anti-inflammatory drugs such as ibuprofen, diclofenac, piroxicam and angiotensin II blockers such as losartan are principally metabolised by CYP2C9 (detailed information on the substrates, inhibitors and inducers of clinically relevant cytochromes P450 is available at http://medicine.iupui.edu/flockhart/). The activity of CYP2C9 is inducible by rifampicin, barbiturates, carbamazepine and ethanol. The resulting increase in substrate's elimination rate mostly attenuates the pharmacological effect of the drug. On the other hand, many drugs such as amiodarone, fluconazole, phenylbutazone, sulphinpyrazone, sulphaphenazole and certain other sulphonamides have been reported to inhibit CYP2C9 activity. The resulting elevation of plasma concentration of parent compound may lead to serious adverse drug effects and toxicity (10).

Two single nucleotide polymorphisms (SNPs) affecting the *CYP2C9* gene have been unambiguously related to impaired drug metabolism (10). The substitution of C416T in exon 3 of *CYP2C9*2* allele results in Arg144Cys (11), whereas A1061C in exon 7 of *CYP2C9*3* allele results in Ile359Leu substitution (12). The functional wild-type allele is classified as *CYP2C9*1*. Recently, some other polymorphisms of this gene have been detected (see http://www.imm.ki.se/CYPalleles/). To date, several *in-vitro* and *in vivo* studies have indicated that the *CYP2C9*2* and *CYP2C9*3* alleles are both associated with decreased metabolic capacity for their substrates (4, 11–16).

Interethnic differences in *CYP2C9* allele distribution have been described. Among African-American and Oriental populations, more than 95% of individuals carry the wild-type genotype (*1/*1). Among Caucasian populations, approximately two-thirds of individuals have the wild-type genotype, while one-third carries either the *1/*2 or *1/*3 genotype. Less than 2.5% of Caucasian individuals carry the *2/*2, *2/*3 and *3/*3 genotype which make them poor metabolizers of CYP2C9 substrates. Gender-specific differences were not apparent in the distribution of polymorphic alleles in these populations (17).

CYP2C19 is involved in the metabolism of antiepileptics such as mephenytoin, diazepam and phenobarbitone, proton pump inhibitors such as omeprazol, certain antidepressants such as imipramine, barbiturate derivates such as hexobarbital and the antimalarial drugs progauanil and chloroproguanil (9). Certain drugs, such as ketoconazole, cimetidine, fluvoxamine, and fluoxetine, have been reported to inhibit CYP2C19 (18). Increased metabolism of CYP2C19 substrates has been shown after treatment of patients with carbamazepine, rifampicin and some others drugs.

The predominant genetic polymorphisms in CYP2C19 are two null alleles, which result in impaired metabolism of CYP2C19 substrates. The substitution of G681A in exon 5 of *CYP2C19*2* variant allele creates an aberrant splice site resulting in an alteration of the reading frame of mRNA and truncated nonfunctional protein (19). The substitution of G636A in exon 4 of *CYP2C19*3* allele results in a premature stop codon, which is common in Oriental populations but very rare in Caucasians (20). Some other rare alleles have been identified (see http://www.imm.ki.se/CYPalleles/). PMs of CYP2C19 represent approximately 3–5% of Caucasians (21). Higher frequencies of PMs (13–23%) are found in most Asian populations (20).

The aim of this study was to determine the frequencies of polymorphic *CYP2C9* and *CYP2C19* alleles in Slovenian population and compare them to that reported for other Caucasians. This information is important to estimate the proportion of the Slovenian population that might experience adverse drug reactions due to genetic polymorphism of *CYP2C9* and *CYP2C19*.

Subjects and methods

DNA samples from 129 unrelated healthy subjects were obtained from the Blood Transfusion Centre of Slovenia (n = 40) and University Children's Hospital in Ljubljana (n = 89). Both groups were sampled to represent the Slovenian population and consisted of hospital and university staff and medical students. Participants in the study were not selected according to age, gender or any other criteria since genotype distribution is not confounded by these factors. The study was approved by the Slovenian Ethics Committee for Research in Medicine.

Genotyping of *CYP2C9*2* and *CYP2C9*3* was performed by polymerase chain reaction (PCR) followed by restriction enzyme analysis, as validated by Yasar et al. (1999). *CYP2C9*2* was analysed by amplification of a fragment having an *Ava*II restriction site present in the wild-type allele but absent in the *CYP2C9*2* allele because of the C416 T mutation. For analysis of the *CYP2C9*3* allele, two different forward primers were used to generate products which both cover polymorphic sequence in exon 7. One of the primers would generate a *Nsi*I site from the wild-type allele, while the other forward primer would generate a *Kpn*I site from the *CYP2C9*3* allele (22). PCR-based restriction enzyme tests were also used for the analysis of *CYP2C19*2, CYP2C19*3* and *CYP2C19*4,* as described by Goldstein and Blaisdell (1996) (23), and Ferguson et al. (1998) (24). The *CYP2C19*2* allele was analysed by amplification of exon 5 followed by digestion with *Sma*I which cleaves the wild-type sequence but does not cleave the *CYP2C19*2* allele. Similarly, the PCR fragments from the amplification of exon 4 were digested with *Bam*HI which cleaves the wild-type sequence but not the *CYP2C19*3* allele (23). The *CYP2C19*4* allele was analysed by amplification of exon 1 using primer that introduces a *Pst*I site only in the *CYP2C19*4* allele (24). The examples of restriction analysis of amplification products are shown in Figure 1.

Results

All of 129 DNA samples were successfully amplified and digested with appropriate restriction enzymes. Five different *CYP2C9* genotypes were identified in the sample represent-

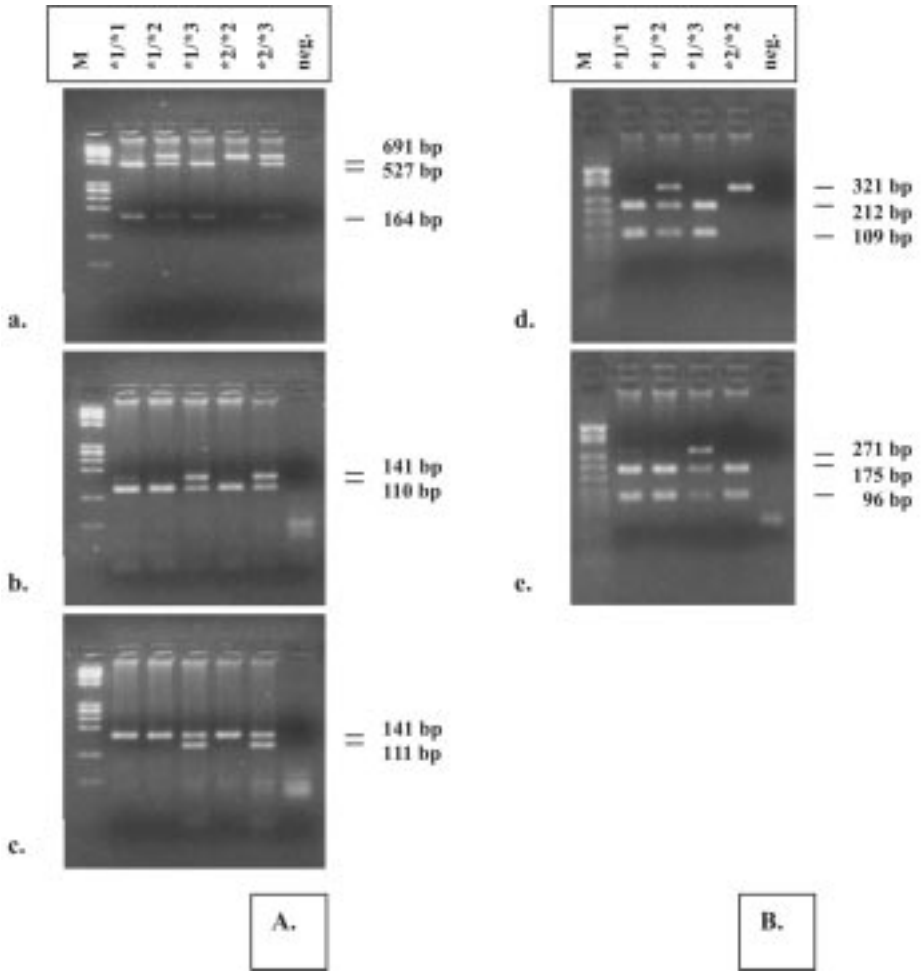

Figure 1. *PCR-based restriction enzyme analysis for CYP2C9 and CYP2C19 alleles. (A) The 691-bp fragment of exon 3 of CYP2C9 gene was amplified by PCR, followed by AvaII digestion (a). The 141-bp PCR products of exon 7 of CYP2C9 gene were digested by NsiI (b) and KpnI (c), respectively. (B) The 321-bp PCR product of exon 5 of CYP2C19 gene was digested by SmaI (d). The 271-bp PCR product of exon 4 of CYP2C19 gene was digested by BamHI (e). Molecular weight markers (M) were: φX174 DNA digested by HaeIII (A) and pUC18 digested by HpaII (B). All fragments were separated on 3% agarose gel.*

Sl. 1. *Restrikcijska analiza pomnoženih fragmentov CYP2C9 in CYP2C19. (A) Eksson 3 gena CYP2C9 smo pomnožili z reakcijo PCR in nato 691 bp dolg produkt cepili z encimom AvaII (a). Pomnoženi fragment eksona 7 gena CYP2C9 (141 bp) smo cepili z encimom NsiI (b) oz. KpnI (c). (B) Pomnoženi fragment eksona 5 oz. eksona 4 gena CYP2C19 (321 bp oz. 271 bp) smo cepili z encimom SmaI (d) oz. BamHI (e). Uporabili smo dolžinske standarde: φX174 DNK, razcepljena s HaeIII (A) in pUC18, razcepljen z HpaII (B). Vse fragmente smo ločili na 3% agaroznem gelu.*

ing Slovenian population (Table 1a). Two-thirds of healthy individuals (n = 86) were homozygous for the wild-type allele and one-third (n = 43) carried at least one polymorphic allele. Two subjects were homozygous for *CYP2C9*2* allele and two subjects were compound heterozygous for *CYP2C9*2* and *CYP2C9*3* allele. No subject homozygous for *CYP2C9*3* allele was detected. The frequency of polymorphic *CYP2C9*2* and *CYP2C9*3* alleles were 0.12 and 0.06, respectively (Table 1b). These frequencies were similar to those reported for other Caucasian populations (Table 2).

When the samples were analysed for *CYP2C19* polymorphism, four different genotypes were detected. Approximately two-thirds of the individuals (n = 88) were homozygous for the wild-type allele. Almost one-third was heterozygous for *CYP2C19*2* allele (n = 39) while only one individual was heterozygous carrier of *CYP2C19*3* allele. One subject homozygous for *CYP2C19*2* allele and none for *CYP2C19*3* allele were identified (Table 1a). No subject carrying *CYP2C19*4* allele was detected in Slovenian population. The frequencies of *CYP2C19*2* and *CYP2C19*3* alleles were determined as 0.159 and 0.004, respectively (Table 1b). These frequencies were similar to those reported for other Caucasian populations as well (Table 3).

Applying Hardy-Weinberg equation, predicted *CYP2C9* and *CYP2C19* genotype frequencies were calculated from observed allele frequencies. The predicted frequencies were not significantly different from the observed frequencies. This means that the population was in Hardy-Weinberg equilibrium.

Discussion

The identification of decreased metabolic activity in polymorphic CYP2C9 and CYP2C19 stimulated a number of investigations to find out the distribution of genetic polymorphisms in different populations.

Of the 129 individuals from Slovenian population analysed in our study, one-third (n = 43) carried at least one of the defective *CYP2C9* alleles, among them four individuals (3.2% altogether) had both alleles defective. The frequencies of *CYP2C9*2* and *CYP2C9*3* in our population were 0.122 and 0.063, respectively, and were similar to those in other Caucasian populations. Only in Spanish population the prevalence of the *CYP2C9*2* and *CYP2C9*3* alleles appears to be greater (25). In contrast to Caucasians, the variant alleles are virtually non-existent in Orientals (26), Africans (27) and African-Americans (12).

The most frequent *CYP2C19* alleles in Caucasian individuals are *CYP2C19*1* and *CYP2C19*2* whereas *CYP2C19*3* and *CYP2C19*4* are extremely rare or absent. Higher allelic *CYP2C19*3* frequency was observed in the Oriental populations (20, 28). Almost one-third of Slovenian individuals analysed (n = 41) carries at least one *CYP2C19* polymorphic allele. The frequencies of *CYP2C19*2* and *CYP2C19*3* alleles in Slovenian population were 0.159 and 0.004, respectively, which is comparable to other Caucasian populations. The fact that we didn't detect any *CYP2C19*4* allele is not surprising since reported frequency of this allele in other Caucasians was also very low (0.006) (24).

The CYP2C9 and CYP2C19 genetic polymorphisms were shown to be clinically important in patients treated with drugs having a narrow therapeutic index (4–7). The results of our study indicate that approximately one-third of individuals from Slovenian population may require either adjustments of dose or increased monitoring when initiating treatment with CYP2C9 and CYP2C19 substrates having a narrow therapeu-

Table 1. *CYP2C9 and CYP2C19 genotypes (a) and allele frequencies (b) in the healthy Slovenian population.*

Razpr. 1. *Genotip (a) in frekvence alelov (b) CYP2C9 in CYP2C19 pri zdravi slovenski populaciji.*

a)

CYP2C9 genotype / Genotip *CYP2C9*	Number / Število	Observed (predicted)* frequency (%) / Ugotovljena (pričakovana)* frekvenca (%)	*CYP2C19* genotype / Genotip *CYP2C19*	Number / Število	Observed (predicted)* frequency (%) / Ugotovljena (pričakovana)* frekvenca (%)
*1/*1	86	66.6 (66.9)	*1/*1	88	68.2 (70.0)
*1/*2	25	19.4 (19.6)	*1/*2	39	30.2 (26.6)
*1/*3	14	10.8 (10.1)	*1/*3	1	0.8 (0.7)
*2/*2	2	1.6 (1.4)	*2/*2	1	0.8 (2.5)
*2/*3	2	1.6 (1.5)	*2/*3	0	0.0 (0.1)
*3/*3	0	0.0 (0.4)	*3/*3	0	0.0 (0.002)
Total / Skupaj	129	100	Total / Skupaj	129	100

b)

CYP2C9 alleles / Aleli *CYP2C9*	Number / Število	Frequency / Frekvenca	*CYP2C19* alleles / Aleli *CYP2C19*	Number / Število	Frequency / Frekvenca
*1	207	0.815	*1	216	0.837
*2	31	0.122	*2	41	0.159
*3	16	0.063	*3	1	0.004
Total / Skupaj	254	1.000	Total / Skupaj	254	1.000

* Predicted frequencies calculated according to the Hardy-Weinberg equation.
* Pričakovane vrednosti so bile izračunane po Hardy-Weinbergovi enačbi.

Table 2. *The distribution of the CYP2C9 allele frequencies in European Caucasian populations.*

Razpr. 2. *Porazdelitev frekvenc alelov CYP2C9 v evropskih populacijah.*

Number of subjects / Število preiskovancev	CYP2C9 allele frequencies Frekvence alelov CYP2C9 *1	*2	*3	Reference / Literatura
British / Britanci				
561	0.841	0.106	0.052	Taube et al. (6)
German / Nemci				
367	0.815	0.107	0.078	Ackermann et al. (29)
Italian / Italijani				
157	0.796	0.112	0.092	Scordo et al. (27)
180	0.739	0.178	0.083	Margaglione et al. (7)
Spanish / Španci				
157	0.694	0.143	0.162	Garcia-Martin et al. (25)
Swedish / Švedi				
430	0.819	0.107	0.074	Yasar et al. (22)
Turkish / Turki				
499	0.794	0.106	0.100	Aynacioglu et al. (30)
Slovenian / Slovenci				
127	0.815	0.122	0.063	present study / pričujoča študija

tic index. High risk of adverse drug reaction may be expected in 1–3% of eventual patients. It is of potential clinical importance to be able to identify individuals who have decreased metabolism for CYP2C9 and CYP2C19 substrates when aiming for rational and individualised pharmacotherapy.

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Table 3. *The distribution of CYP2C19 allele frequencies in European Caucasian populations.*

Razpr. 3. *Porazdelitev frekvenc alelov CYP2C19 v evropskih populacijah.*

Number of subjects / Število preiskovancev	CYP2C19 allele frequencies Frekvence alelov CYP2C19 *1	*2	*3	Reference / Literatura
Danish / Danci				
239	0.839	0.161	0.000	Bathum et al. (31)
64	0.820	0.180	0.000	Bathum et al. (31)
German / Nemci				
140	0.850	0.150	NT	Brockmoller et al. (32)
Portugese / Portugalci				
153	0.869	0.131	NT	Ruas and Lechner (33)
Swedish / Švedi				
160	0.834	0.166	NT	Chang et al. (34)
83	0.849	0.145	0.006	Yamada et al. (35)
162	0.852	0.148	0.000	Yamada et al. (35)
Slovenian / Slovenci				
127	0.837	0.159	0.004	present study / pričujoča študija

NT – not tested / ni testirano

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