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Prevalence of five pharmacologically most important *CYP2C9* and *CYP2C19* allelic variants in the population from the Republic of Srpska in Bosnia and Herzegovina

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The enzymes of the cytochrome P450 superfamily play a critical role in phase I drug metabolism. Among them, CYP2C9 and CYP2C19 are clinically important, as they can mediate severe toxicity, therapy failure, and increased susceptibility to cancer and other diseases caused by chemicals. The aim of this study was to determine the prevalence of pharmacologically most important allelic variants of the *CYP2C9* and *CYP2C19* genes in the general population of the Republic of Srpska (Bosnia and Herzegovina) and to compare them with other populations. For this purpose we determined the genotype profile and allele frequency of 216 randomly selected healthy volunteers using real-time polymerase chain reaction (RT-PCR). The prevalence of the *CYP2C9 *2* and **3* alleles was 13.6 and 7.4 %, respectively. Based on these frequencies, of the 216 participants four (1.86 %) were predicted to be poor metabolisers, 78 (36.11 %) intermediate, and the remaining 134 (62.03 %) normal metabolisers. Based on the prevalence of *CYP2C19 *2* and **17* variants – 16.2 and 20.4 %, respectively – nine (4.17 %) were predicted to be poor, 57 (26.39 %) rapid, and nine (4.17 %) ultra-rapid metabolisers. We found no significant differences in allele frequencies in our population and populations from other European countries. These findings suggest that genetically determined phenotypes of *CYP2C9* and *CYP2C19* should be taken into consideration to minimise individual risk and improve benefits of drug therapy in the Republic of Srpska.

KEY WORDS: cytochrome P450 enzymes; pharmacogenetics; polymorphic allele

The cytochrome P450 (CYP) superfamily consists of enzymes with highly diverse roles in the metabolism of drugs, fatty acids, steroids, and xenobiotics (1, 2). Their genetic variants, single nucleotide polymorphisms (SNPs) in particular, can lead to therapy failure, severe toxicity, and increased susceptibility to cancer and other diseases caused by chemicals (3). CYPs make about 80 % of all drug metabolising enzymes (DMEs), most notably those participating in phase I metabolism, such as flavin-containing monooxygenases, epoxide hydrolases, and many other oxidising, reducing, and hydrolysing enzymes (4).

Bearing in mind various types of mutation caused by SNPs, genotyping the most relevant CYP enzymes could identify patients at risk of developing adverse drug reactions and increase treatment safety and efficiency (3). In this respect, CYP enzymes CYP2C9 and CYP2C19 are among clinically most relevant, as they metabolise about 20–30 % of all drugs (5). CYP2C9 metabolises over 100 drugs or about 15 % of all drugs in current use (6, 7) including oral anticoagulants, nonsteroidal anti-inflammatory drugs, angiotensin II receptor antagonists, antidiabetic drugs, antiepileptics, and alkylating anticancer prodrugs (7–9). Clinically the most interesting allelic variants of *CYP2C9* are **2* and **3* (10). The **2* allele is categorised as a loss-of-function variant, and the **3* allele as a no-function variant, based on data obtained from studies conducted on multiple substrates, including flurbiprofen, celecoxib, phenytoin, and warfarin (9). Accordingly, an individual's ability to metabolise CYP2C9 substrates can be classified into the following phenotypes: normal metaboliser *(*1/*1* genotype), intermediate metaboliser *(*1/*1*; **1/*3*; and **2/*2* genotype), and poor metaboliser *(*2/*3* and **3/*3* genotype) (11). Since the prevalence of poor metabolisers in Caucasian population is 3–5 %, genotyping of *CYP2C9*2* and **3* could be very important in initial dose adjustment in patients requiring anticoagulant therapy, such as warfarin (12, 13).

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CYP2C19 metabolises 8–10 % of commonly used drugs such as proton pump inhibitors, anticonvulsant drugs, antiplatelet drugs, and antidepressants (14, 15). Besides the wild-type **1* allele, the most common allelic variant is the loss-of-function *CYP2C19*2*, characterised by reduced enzyme activity (6, 14). Its prevalence in European populations is 16 %, in Africa 14 %, and in Asia 26 %.

Genotyping for the *CYP2C19* allelic variant **3* is important in clinical practice, since its carriers have no ability to metabolise substrates completely, which may lead to drug accumulation in the body (16). Individuals carrying these two loss-of-function alleles (e.g. *2/*2, *2/*3, *3/*3) are therefore characterised as poor metabolisers (8). However, allelic variant **3* is very rare in Europeans and Africans (1 %) but not as rare in Asians (8 %) (15, 17).

In contrast to the *2 allelic variant, a recently identified *CYP2C19*17* variant increases transcriptional activity, and individuals carrying one wild-type (normal function) allele and one gain-of-function variant (**1/*17*) are categorised as rapid metabolisers (12, 18), whereas those carrying two gain-of-function variants (**17/*17*) are classified as ultra-rapid metabolisers (19). Determining whether a person is a carrier of the *CYP2C19*17* polymorphism could therefore be very important in clinical practice, since clopidogrel has increased efficacy in these carriers and increases their risk of bleeding (14, 20).

Considering that no genotyping of these important allele variants of *CYP2C9* and *CYP2C19* has been conducted in the Republic of Srpska in Bosnia and Herzegovina, the aim of our study was to fill that gap and also compare our findings with other populations.

MATERIALS AND METHODS

Our study included 216 randomly selected Caucasian healthy volunteers from the general population of the Republic of Srpska, which is one of the federal entities located in the northern and eastern part of Bosnia and Herzegovina, with a population of about 1.2 million (21). The sample was recruited to reflect population distribution from all over the Republic of Srpska. It consisted of 114 men (53 %) and 102 (47 %) women aged between 18 and 78 years (median: 41). The study was approved by the Ethics Committee of the University of Banja Luka Faculty of Medicine. All participants signed informed consent forms before inclusion. The exclusion criteria were serious mental or physical illnesses. The study was performed according to the Declaration of Helsinki.

Genotyping

Genetic analysis was done at the Laboratory for Molecular Biology and Genetics of the University of Banja Luka Faculty of Medicine Center for Biomedical Research. Genomic DNA was extracted from 3–6 mL of peripheral blood collected in Na-EDTA tubes using PureLink® gDNA Blood Kit (Invitrogen, Carlsbad, CA, USA). Genotypes of *CYP2C9 *2* (3608C>T, rs1799853), *CYP2C9*3* (42164A>C, rs1057910), *CYP2C19*2* (681G>A, rs4244285), *CYP2C19*3* (17948G>A, rs4986893), and *CYP2C19*17* (-806C>T, rs12248560) were determined with real-time polymerase chain reaction (RT-PCR) using TaqMan® drug metabolism genotyping assays (C_25625805_10, C_27104892_10, C_25986767_70, C_469857_10, and C_27861809_10, respectively) according to the manufacturer's instructions (Applied Biosystems, Foster City, CA, USA). PCR conditions included initial denaturation/polymerase activation at 95 °C for 10 min, followed by 50 two-step cycles: denaturation at 95 °C for 15 s and annealing and extension at 60 °C for 90 s. The results were analysed with the Applied Biosystems 7500 software v2.0.6 (Applied Biosystems).

Statistical analysis

Allele and genotype prevalences were estimated by gene counting. Genotype distributions were tested for the Hardy-Weinberg equilibrium. Chi-squared test with Yate's correction was used to test similarities or differences in allele distribution. For all analyses we used the Social Science Statistics online calculators (https://www.socscistatistics.com/tests/).

RESULTS AND DISCUSSION

CYP2C9

As expected, the wild-type *CYP2C9*1* dominated (78.90 %), followed by the *CYP2C9*2* variant (13.66 %),

Table 1 Genotype and predicted phenotype prevalences of the *CYP2C9* allelic variants in the population of the Republic of Srpska

Genotype	Participants (N)	Prevalence (%)	Confidence interval (95 %)	Predicted phenotype
*CYP2C9*1/*1*	134	62.03	55.20–68.53	normal metabolisers
*CYP2C9*1/*2*	47	21.76	16.45–27.86	intermediate metabolisers
*CYP2C9*1/*3*	26	12.04	8.02–17.14	intermediate metabolisers
*CYP2C9*2/*2*	5	2.31	0.76–5.32	intermediate metabolisers
*CYP2C9*2/*3*	2	0.93	0.11–3.30	poor metabolisers
*CYP2C9*3/*3*	2	0.93	0.11–3.30	poor metabolisers

Table 2 Genotype and predicted phenotype prevalences of the CYP2C19 allelic variants in the population of the Republic of Srpska

Genotype	Participants (N)	Prevalence (%)	Confidence interval (95 %)	Predicted phenotype
*CYP2C19*1/*1*	89	41.20	34.57–48.08	normal metabolisers
*CYP2C19*1/*2*	39	18.05	13.17–23.85	intermediate metabolisers
*CYP2C19*2/*17*	13	6.02	3.24–10.07	intermediate metabolisers
*CYP2C19*1/*3*	-	-	-	intermediate metabolisers
*CYP2C19*3/*17*	-	-	-	intermediate metabolisers
*CYP2C19*2/*2*	9	4.17	1.92–7.76	poor metabolisers
*CYP2C19*3/*3*	-	-	-	poor metabolisers
*CYP2C19*2/*3*	-	-	-	poor metabolisers
*CYP2C19*1/*17*	57	26.39	20.64–32.80	rapid metabolisers
*CYP2C19*17/*17*	9	4.17	1.92–7.76	ultra-rapid metabolisers

while the prevalence of the *CYP2C9*3* allele was 7.40 % (Table 1). All observed genotype frequencies were in the Hardy-Weinberg equilibrium. Accordingly, the most prevalent (62.03 %) were normal metabolisers *(*1/*1* genotype). Poor metabolisers (**2/*3* and **3/*3* genotype) accounted for 1.86 %, and intermediate metabolisers (**1/*2*, **1/*3* or **2/*2* genotype) for 36.11 % of participants.

The prevalences of *CYP2C9*2* and *CYP2C9*3* alleles found in our study are similar to the respective ones reported in other European countries such as Germany (14.0 %; p=0.29 and 5 %; p=0.37) (20), Russia (10.5 %; p=0.16 and 6.7 %; p=0.78) (22), Spain (16 %; p=0.36 and 10 %; p=0.25) (23), Greece (12.9 %; p=0.80 and 8.13 %; p=0.58) (24), North Macedonia (13.9 %; p=0.91 and 7.3 %; p=0.94) (17), Croatia (14.5 %; p=0.65 and 7.6 %; p=0.89) (8), Serbia (11.7 %; p=0.30 and 8.1 %; p=0.68) (25), and Slovenia (12.2 %; p=0.54 and 6.3 %; p=0.55) (26). However, one Romanian study (27) showed significantly higher prevalence of the **2* and **3* alleles (29 %, p<0.0001 and 20.2 %; p<0.0001, respectively). The general prevalences of the *CYP2C9*2* and **3* alleles in the Caucasian population are about 13 % (**2*) and 7 % (**3*) (28) but significantly lower in the East Asians (0.01 % and 0.3 %), Africans (2 % and 1 %), and African-Americans (1 % and 0.5 %) (29, 30). A more detailed comparison is available in Table 3.

CYP2C19

Again, the wild-type *CYP2C19*1* allele was the most prevalent (63.43 %), followed by *CYP2C19*2* (16.20 %) and *CYP2C19*17* (20.37 %) (Table 2). The observed prevalence of the **2* and **17* allelic variants were within the European ranges (8, 18). Similar prevalences have been reported for the neighbouring countries. In the Serbian population the prevalence of the **2* allele was 16.3 % (p=0.97) and of the **17* allele 22.2 % (p=0.45). In the Croatian population it was 14.8 % (p=0.50) and 23.7 % (p=0.19), in the North Macedonian 14.4 % (p=0.48) and 20.1 % (p=0.93), and in the population of Kosovo 13.03 % (p=0.18) and 19.01 % (p=0.61), respectively (8, 17, 25, 30). However, Russian and Greek studies showed a significant difference in the **2* allele prevalence (p=0.0002 and p=0.0035, respectively) (22, 24). A more detailed comparison is given in Table 3.

Eighty-nine participants (41.20 %) with the *CYP2C19*1/*1* genotype were normal metabolisers, 52 (24.07 %) with the *CYP2C19*1/*2* and *CYP2C19*2/*17* genotypes were intermediate metabolisers, nine (4.17 %) with the *CYP2C19*2/*2* genotype were poor metabolisers, 57 (26.39 %) with the *CYP2C19*1/*17* genotype rapid metabolisers, and nine (4.17 %) with the *CYP2C19*17/*17* genotype were ultra-rapid metabolisers. Carriers of the *CYP2C19*17* allele are at risk of bleeding, especially the ultra-rapid metabolisers (carriers of the *CYP2C19*17/*17* genotype) (18). Carriers of the *CYP2C19*2/*17* genotype are generally considered intermediate metabolisers, but their metabolic phenotype is difficult to predict, since some data suggest that *CYP2C19*17* may not compensate for the *CYP2C19*2* allele (8).

As for the *CYP2C19*3* allele, none was detected in this study, which corresponds to other Caucasian populations such as Croatian, Danish, Canadian, German, Polish, and Australian (4, 31–35).

CONCLUSION

In summary, our data confirmed similar prevalences of the five *CPY2C9* and *CYP2C19* polymorphisms in the population of the Republic of Srpska with other European populations. Although our findings are based on a relatively small sample size, these data could be useful in assessing the risks and benefits of drug therapy in individuals requiring anticoagulant therapy, such as warfarin and clopidogrel.

Conflict of interests

None to declare.

Table 3 Genotype and the prevalence of the *CYP2C9* and *CYP2C19* allelic variants in the population of the Republic of Srpska (RS) compared to other populations

				Alleles frequencies																		
Gene	**Genotype**	**Genotype frequency n (%)**	**Alleles**	**RS**	**Bosnia and Herzegovina**	**Macedonia**	**Croatia**	**Serbia**	**Kosovo**	**Slovenia**	**Italy**		**Greece**	**Germany**	**Russia**	**Spain**	**Eastern Asians**	**African**	**African-American**
	References				(36)	(37)	(17)	(8)	(38)	(25)	(30)	(26)	(39)	(40)	(41)	(24)	(20)	(22)	(23)	(16)	(29)	(29)
*CYP2C9*2*	**1/*1*	162 (75)	C	0.866	0.868	0.910	0.861	0.855	0.835	0.883	0.825	0.878	0.830	0.846	0.875	0.896	0.860	0.895	0.840	0.999	0.980	0.990
	**1/*2*	46 (21.29)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	**2/*2*	5 (2.31)	T	0.134	0.132	0.090	0.139	0.145	0.165	0.117	0.175	0.122	0.170	0.154	0.125	0.104	0.140	0.105	0.160	0.0001	0.020	0.010
*CYP2C9*3*	**1/*1*	186 (86.11)	A	0.928	0.911	-	0.927	0.924	0.905	0.919	0.891	0.937	0.856	0.916	0.903	0.933	0.950	0.933	0.900	0.997	0.990	0.995
	**1/*3*	28 (12.96)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	**3/*3*	2 (0.93)	C	0.072	0.089	-	0.073	0.076	0.095	0.081	0.109	0.063	0.144	0.084	0.097	0.067	0.050	0.067	0.100	0.003	0.010	0.005
*CYP2C19*2*	**1/*1*	155 (71.76)	G	0.847	-	0.830	0.856	0.852	0.850	0.837	0.870	0.841	-	0.907	0.889	0.869	-	0.886	-	-	-	-
	**1/*2*	52 (24.07)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	**2/*2*	9 (4.17)	A	0.153	-	0.170	0.144	0.148	0.150	0.163	0.130	0.159	-	0.093	0.111	0.131	-	0.114	-	-	-	-
*CYP2C19*3*	**1/*1*	216 (100)	G	1.00	-	-	-	-	-	-	-	0.996	-	-	1.00	1.00	-	0.997	-	-	-	-
	**1/*3*	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	**3/*3*	0	A	0.00	-	-	-	-	-	-	-	0.004	-	-	0.00	0.00	-	0.003	-	-	-	-
*CYP2C19*17*	**1/*1*	137 (63.42)	C	0.796	-	-	0.799	0.763	-	0.778	0.810	-	-	0.776	-	-	-	-	-	-	-	-
	**1/*17*	70 (32.41)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	**17/*17*	9 (4.17)	T	0.204	-	-	0.201	0.237	-	0.222	0.190	-	-	0.224	-	-	-	-	-	-	-	-

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Prevalencija pet farmakološki najznačajnijih *CYP2C9* i *CYP2C19* alelenih varijanti u populaciji Republike Srpske u Bosni i Hercegovini

Citokrom P450 (CYP) visokopolimorfna je superobitelj enzima s ključnom ulogom u metabolizmu lijekova, masnih kiselina, steroida i ksenobiotika. U okviru spomenute skupine enzimi CYP2C9 i CYP2C19 prepoznati su kao klinički važni jer sudjeluju u prvoj fazi metabolizma lijekova te mogu dovesti do neadekvatnoga terapijskog odgovora, toksičnosti i pojave određenih bolesti. Cilj istraživanja je bio odrediti genotipove i prevalenciju alela u 216 nasumice odabranih zdravih ispitanika u populaciji Republike Srpske (Bosna i Hercegovina), te rezultate usporediti s drugim populacijama. Genotipovi enzima CYP2C9 i CYP2C19 određeni su metodom lančane reakcije polimeraze u realnom vremenu (eng. *real-time PCR*). Prema protokolu proizvođača, korištene su Taqman početnice i probe (engl. *Taqman SNP genotyping assay*). Kod *CYP2C9*, učestalosti alela *2 i *3 su 13,6 odnosno 7,4 %. Od 216 sudionika, njih četvero (1,86 %) spori su metabolizatori, a većina njih (62,03 %) normalni metabolizatori. Što se tiče *CYP2C19*, učestalosti alela *2 i *17 su 16,2 odnosno 20,4 %. Od ukupnoga broja sudionika, njih devet (4,17 %) spori su metabolizatori, njih 57 (26,39 %) brzi metabolizatori, a devet je sudionika (4,17 %) okarakterizirano kao ultrabrzi metabolizatori. U usporedbi s podatcima o učestalosti genotipova i alelnih varijanti *CYP2C9* i *CYP2C19* u drugim europskim populacijama, dobiveni rezultati pokazali su veliku sličnost. Rezultati ovog istraživanja upućuju da bi određene terapije trebale uzeti u obzir utvrđene fenotipove *CYP2C9* i *CYP2C19* prilikom procjene individualnih rizika i dobrobiti primjene.

KLJUČNE RIJEČI: enzimi citokroma 450; farmakogenetika; polimorfizam alela