Prevalence of five pharmacologically most important \textit{CYP2C9} and \textit{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 \textit{CYP2C9} and \textit{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 \textit{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 \textit{CYP2C9} *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 \textit{CYP2C9} and \textit{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 \textit{CYP2C9} and \textit{CYP2C19} should be taken into consideration to minimise individual risk and improve benefits of drug therapy in the Republic of Srpska.
CYP2C19 metabolises 8–10 % of commonly used drugs such as proton pump inhibitors, anticonvulsant drugs, antplatelet 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 (*1/*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), CYP2C9*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 %),
However, Russian and Greek studies showed a significant (p=0.18) and 19.01 % (p=0.61), respectively (8, 17, 25, 30). In the population of Kosovo 13.03 % (p=0.93), and in the population of Kosovo 13.03 % (p=0.93) and 23.7 % (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 CYP2C9 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 frequences | RS | Bosnia and Herzegovina | Croatia | Serbia | Slovenia | Italy | Greece | Germany | Russia | Spain | Eastern Asians | Africa | African-American |
|-------------------|----|------------------------|---------|--------|---------|------|-------|---------|--------|-------|----------------|--------|------------------|
| **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) | 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  |
| *2/*2             | 5 (2.31) | T                | 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  |
| **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) | T                | 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  | 0.997  | 0.990  |
| *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/*3             | 0     | -                | -      | -      | -      | -    | -     | -      | -      | -    | -     | -      | -      | -      | -      | -      |
| *2/*2             | 0     | A                | 0.00   | -      | -      | -    | 0.004 | -      | -      | 0.00  | -      | 0.00   | -      | -      | 0.003  | -      |
| **CYP2C19*17**    |    |                        |         |        |         |      |       |         |        |       |                |        |                  |
| *1/*1            | 137 (63.42) | G               | 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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(36) (37) (17) (8) (38) (25) (30) (26) (41) (24) (20) (22) (23) (16) (29) (29) (16) (29) (29) (16) (29) (29)
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Prevalencija pet farmakološki najznačajnijih CYP2C9 i CYP2C19 alelenih varijanti u populaciji Republike Srpske u Bosni i Hercegovini

Citotrom P450 (CYP) visokopolimorfna je superobitelj enzima s ključnom ulogom u metabolizmu lijekova, masnih kiselina, stereoide i ksenobiotika. U okviru spomenute skupine enzima 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 (engl. 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 ukupnog broja sudionika, njih devet (4,17 %) spori su metabolizatori, njih 57 (26,39 %) brzi metabolizatori, a većina njih (62,03 %) normalni metabolizatori. Što se tiče CYP2C19, učestalosti alela *2 i *3 su 16,2 odnosno 10,5 %. Od ukupnog 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 alelenih 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 RJEČI: enzimi citokroma 450; farmakogenetika; polimorfizam alela