the drug developed by integrating the antibiotic organosilicon nanostructure – niosomes having substantial lipophilicity, thus by not sexposing doxorubicin in normal tissues, and only by penetration through the tumor capillaries of the skin defect. The chemical composition of niosomes provides deep transdermal penetration of drugs, in a size of less than 100 nanometers niosomes made invisible to the cells of the reticuloendothelial system, which increases the availability of the encapsulated drug to the target cells. Reduced heart and liver toxicity greatly expand the use of the drug among patients suffering from various chronic diseases. Application niosomal's gel will reduce the likelihood of necrosis at the injection site and other side effects of the drug.

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About authors:

Bazikov Igor Aleksandrovich, MD, Professor, Head of the Department of Microbiology StSMU, Russia; tel.: +7(8652)352475, +79188664027; e-mail: bazikov@list.ru

Chekrygina Elena Vladimirovna, Assistant of the Department of Microbiology StSMU, Russia; tel.: +7(8652)352475, +79094623606

Klimanovich Inna Victorovna, PhD, assistant professor of microbiology StSMU, Russia; tel.: +7(8652)352967, +79624466068

Maltsev Alexander Nikolaevich, PhD, Senior researcher at the Laboratory of nanotechnology drugs StSMU, Russia; tel.: +7(8652)352475

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ROLE OF GENETIC FACTORS IN THERAPY WITH INDIRECT ANTICOAGULANTS IN ETHNIC GROUPS OF STAVROPOL REGION

Baturin V. A., Tsarukyan A. A.

Stavropol State Medical University, Stavropol, Russian Federation

ЗНАЧЕНИЕ ГЕНЕТИЧЕСКИХ ФАКТОРОВ ДЛЯ ТЕРАПИИ НЕПРЯМЫМИ АНТИКОАГУЛЯНТАМИ В ЭТНИЧЕСКИХ ГРУППАХ СТАВРОПОЛЬСКОГО КРАЯ

В. А. Батурин, А. А. Царукян

Ставропольский государственный медицинский университет, Ставрополь, Российская Федерация

The study focused on specific issues about intake of indirect anticoagulants and the impact of the drug response genetic characteristics in representatives of the three ethnic groups residing in the Stavropol Region – Slavs, Armenians, and Karachais. The results showed that reaching the target value of INR in

Armenians took a lower daily dose of Warfarin – 3.9 mg, while in the Karachais and in the Slavs this dosage was 5.1 mg and 5.2 mg, respectively. Of the patients who reached the target level of INR Armenians were prevailing – 57%, while Slavs accounted for 31.7% and Karachais – 33.3%; the number of the patients with a high level of INR (>3) was highest among Armenians – 25.7% (Slavs – 18.3%, Karachais – 11.1%). According to the results of genotyping the maximum frequency of the "slow metabolizers" was detected among the Armenians – 52.6%. Based on the outcomes obtained, identification of CYP2C9 genotypes is recommended to be introduced into the list of compulsory medical studies to be performed in clinical practice.

Key words: Warfarin, CYP2C9, ethnic-bound issues, biotransformation, cytochrome P-450

Проведено изучение особенностей потребления непрямых антикоагулянтов и влияния генетических особенностей на лекарственный ответ у представителей трех этнических групп Ставропольского края: славянской, армянской и карачаевской. В результате было показано: для достижения целевого уровня МНО у армян требовалась более низкая суточная доза варфарина – 3,9 мг, у карачаевцев и славян – 5,1 и 5,2 мг соответственно. Среди пациентов, достигших целевого значения МНО, оказалось достоверно больше представителей армян – 57% по сравнению с группой славян – 31,7% и карачаевцев – 33,3%, и доля пациентов с высоким значением МНО (выше 3) наибольшая в группе армянского этноса – 25,7% (у славян – 18,3%, у карачаевцев – 11,1%). По результатам генотипирования максимальная частота «медленных» метаболизаторов выявлена среди представителей армянской этнической группы – 52,6%. На основании полученных результатов выявление генотипов CYP2C9 рекомендовано включить в перечень обязательных медицинских исследований для применения в клинической практике.

Ключевые слова: варфарин, CYP2C9, этнические особенности, биотрансформация, цитохром P-450

Pharmacological response has been long known to possess individual features both in terms of differences in efficacy and in safety of pharmacotherapy. The reasons behind this may be due to the impact that various factors have on drug metabolism, while these factors can be either modifiable or non-modifiable (the patient's age, gender, body features as well as genetically determined characteristics of pharmacokinetics and pharmacodynamics). The genetic features passed from generation to generation are so-called single nucleotide polymorphisms of genes, which encode proteins participating in the pharmacokinetics or pharmacodynamics of the drug. It is known currently that the most important clinical significance lies within polymorphism of the genes that are responsible for the synthesis and activity of enzymes of a medicinal agent (MA) metabolism, as well as transport proteins that are involved in the major stages of pharmacokinetics [9]. The vast majority of MAs are metabolized in the liver microsomes by the oxygenase system, which is dependent on the activity of cytochrome P-450. The most polymorphic isoenzymes playing a leading role in the processes of metabolism for a number of MAs include *CYP2C9, CYP2D6,* and *CYP2C19* [5]. There are more than 200 allelic variants of cytochromes involved in drug biotransformation [3]. One of the most important and well-studied cytochrome P450 isoform is *CYP2C9,* which metabolizes nearly 16% of MAs including indirect anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin receptor blockers, and oral hypoglycemic MAs.

One of the substrates for CYP2C9 is the group of vitamin K antagonists, or indirect anticoagulants (IDAC), which lead as the agents of choice when it comes to prevention of thromboembolic complications in cardiovascular diseases. Due to a significant body of evidence, IDAC are widely used in clinical practice; however, despite well-developed drug safety control there is still high risk of developing bleeding during treatment with MAs belonging to this group [10]. The frequencies of polymorphic variants in *CYP2C9*2* and *CYP2C9**3 are known to reveal significant interethnic differences. This feature lays the basis for the well-known phenomenon of different frequencies of adverse effects of certain MAs in different races and ethnic groups [6]. Therefore, identification of *CYP2C9* genotypes is important in view of effective results of drug therapy, predicting and preventing the development of unwanted side reactions. The Stavropol Region, if viewed from the stance of ethnopharmacology, is of special interest as the local ethnosphere has historically been developing as polyethnic and multicultural. Mention to be made also that there was earlier research done aiming at detecting specific issues in the effect that various MAs have on residents of the Caucasus Mineral Waters Region, which showed ethnic differences in the effects of antihypertensive and antianginal drugs matching people belonging to the Russian ethnic group and Armenians [1, 12]. Besides there was some difference revealed in the frequencies of the «slow» allelic variants of the *CYP2D6* gene in Slavs, Armenians, and Karachais residing in the Stavropol Region [2].

The purpose of this study was to analyze the specific issues about Warfarin intake in people of the following three ethnic groups of the Stavropol Region: Slavs (ethnic Russians and Ukrainians), Armenians, and Karachais, and to evaluate the role of genetic peculiarities of these ethnic groups in the development of drug response.

Material and Methods. The study involved 22 patients with persistent atrial fibrillation taking Warfarin. Out of this body of patients Slavs were 60, Armenians – 35, Karachais – 27. The examined groups were matched by age and gender. The mean age of the patients was 58.5±9 yrs. Comorbidities were coronary artery disease, hypertension (stages 1 and 2), chronic heart failure (functional classes I and II). The patients enrolled in the study took Warfarin in various doses (0.625 mg to 12.5 mg) to achieve the target INR (2–3).

The investigation of the prevalence of allelic variants of the *CYP2C9* gene included volunteers (total number – 136) from among Stavropolities: 63 Slavs, 38 Armenians, and 35 Karachais. The allelic variants of the gene were detected by PCR using diagnostic kits to detect polymorphisms in the human genome SNP – EXPRESS (Research Company Lytech, Moscow, Russia). The analysis was performed on human genomic DNA isolated from whole blood leukocytes with the reagent DNA-Express-Blood (Research Company Lytech). Each sample of isolated DNA was subject to two amplification reactions – with two pairs of allele-specific primers. The work was done employing the amplifier Tertsik (DNA-Technology, Russia). The focus was on detecting the frequency of the first two most significant allelic variants of the *CYP2C9* gene typical of European race: *CYP2C9*2* and *CYP2C9*3* [11]. During that, the activity of *CYP2C9* in *CYP2C9*2* allelic variant carriers is 18% of the norm while in the carriers of the *CYP2C9*3* allelic variant it is 5% only [8]. Genotyping was performed by electrophoretic detection. The ethnic belonging was verified based on the data provided by the participants implying absence of interethnic marriages down to the third generation.

The obtained data were processed using the statistical software package SPSS 21.0 for Windows employing the methods of parametric and non-parametric statistics. The work included a descriptive analysis of all the patients enrolled. The qualitative variables were described as absolute and relative (%) frequencies; for the quantitative variables the mean, standard deviation, and standard error of the mean were calculated. The t-test for independent samples was used to compare the two groups with normal data distribution while for the non-normal distributions the χ^2 test was required. The significance of the differences in allele frequencies between the studied groups was assessed through the Kruskal-Wallis test and ANOVA. For all the types of the analysis the differences were considered statistically significant at $p < 0.05$.

Results and Discussion. Among the patients whose INR reached the target value (2–3) Armenians accounted for a significantly higher number (p0.05) – 20 persons (57%) compared to Slavs – 19 patients (31.7%) and Karachais – 9 persons (33.3%). A significant group of the patients who were taking Warfarin did not reach the therapeutic values of INR. The group of Armenians had significantly fewer of such patients ($p<0.05$) – 6 persons (17.3%) in comparison to Slavs and Karachais – 30 (50%) and 15 persons (55.6%), respectively (Table 1).

Table

Distribution of the patients by ethnic groups depending on their INR levels

Ethnic group	INR		
	<2	2–3	>3
Slavs	30 (50%)*	19 (31.7%)**	11 (18.3%)
Armenians	6 (17.3%)*(**)	20 (57%)*(**)	9 (25.7%)**
Karachais	15 (55.6%)**	9 (33.3%)**	3 (11.1%)**

* – $p<0.05$ at comparing INR in Armenians and Slavs (χ^2 test).
** – $p<0.05$ at comparing INR in Armenians and Karachais (χ^2 test).

The mean INR in the Armenians was 2.3±0.7, while in the Slavs and in Karachais the INR showed no difference and was 2.0 in the two groups (Slavs – 2.0±0.9; Karachais – 2.0±0.64) (Figure).

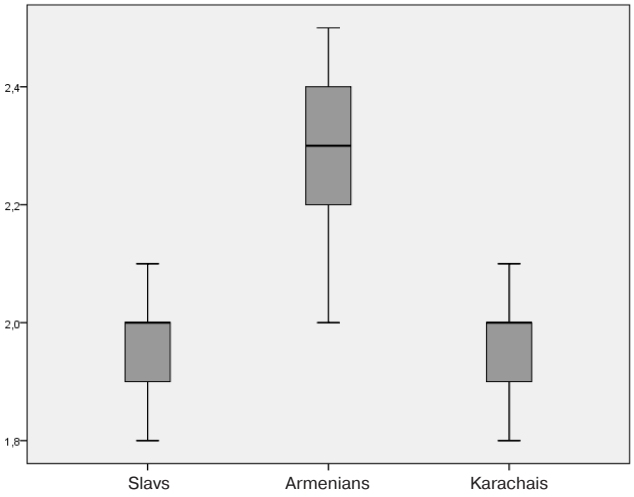

Fig. Mean values of INR in the patients studied

Risk assessment for the complications associated with Warfarin treatment showed that of the 60 patients in the Slavs group 11 persons (18.3%) had episodic increase in their INR above 3. Among the Karachai group similar episodes were registered in 3 patients (11.1%). 9 (25.7%) patients in the group of 35 ethnic Armenians were detected to have episodes of INR increase above 3; given that, such episodes of INR above 3 were significantly more frequent ($p<0.05$) compared to the Karachai patients (Table 1).

To characterize the effectiveness of Warfarin it was deemed important to calculate for the studied groups the average doses of anticoagulant, ensuring target values of INR (2–3). For this purpose only the patients were selected whose INR lay within the target values: 19 (31.7%) of the Slavs, 20 (57%) Armenians, and 9 (33.3%) Karachais. It was shown that to reach the target level of INR in the Armenians it took a lower daily dose of Warfarin – 3.8±1.5 mg, while for the Karachais and the Slavs it was 5.1±1.5 mg and 5.2±2.0 mg, respec-

tively. At the same time, the Armenians (matched against the Slavs and the Karachais) had their Warfarin dosage of less than 5 mg/day administered to them appropriately in a higher number of cases (the difference being statistically meaningful) (Table 2).

Table 2

Distribution of the patients by ethnic groups depending on Warfarin dosage

Warfarin dosage	Slavs n=60	Armenians n=35	Karachais n=27
< 5 mg	13 (21.7%)*	19 (54.3%)*(**)	7 (25.9%)**
> 5 mg	47 (78.3%)*	16 (45.7%)*(**)	20 (74.1%)**

* – $p<0.05$ at comparing Warfarin dosages in Armenians and Slavs (χ^2 test).
** – $p<0.05$ at comparing Warfarin dosages in Armenians and Karachais (χ^2 test).

This suggests a higher efficiency rate of Warfarin in the Armenian ethnic group. The results obtained offer every reason to use individualized approach to the choice of the starting dose of Warfarin depending on the ethnic affiliation of the patient.

According to the results of genotyping, the maximum total rate of «slow metabolizers» was detected among the patients of the Armenian group – 20 persons, which made up 52.6%. The same mutation in the Slavs and the Karachais was observed in 24 (38.1%) and 9 (25.7%) cases, respectively. The frequency of clinically important *CYP2C9*3* allele was significantly different in the Slavs (6.3%) and the Armenians (14.5%), the Slavs and the Karachais (10%), and was prevalent among the Armenians and the Karachais (Table 3).

Table 3

Frequencies of the *CYP2C9*3* allele and significance of the differences in the studied populations

Population	Total number of alleles	*CYP2C9*3* frequency	Slavs	Armenians	Karachais
Slavs	126	6.3 (8 all.)	–	p<0.05	p<0.05
Armenians	76	14.5 (11 all.)	p<0.05	–	p>0.05
Karachais	70	10 (7 all.)	p<0.05	p>0.05	–

The total frequency of *CYP2C9*2* in the different populations varies from 8 to 18%, the frequency of *CYP2C9*3* is 4–10% [8, 11]. The frequencies of alleles detected in the Slavs group are comparable with those in population of Russians and other Europeans. Besides, the Karachais showed the minimum *CYP2C9*2* allele frequency, while the Armenians had *CYP2C9*3* at maximum compared to the Slavs. Research [7] shows that Karachais, if compared to Circassians, possess a genetically determined sensitivity to MA substrates of CYP2C9 (oral anticoagulants, NSAIDs, oral hypoglycemic agents), and, consequently, are predisposed to unwanted side reactions in case of using such substances [7]. When studying the *CYP2C9* gene polymorphism in the aboriginal peoples of North Siberia a certain proportion of «slow metabolizers» was detected in the North Siberian aborigines and Russians – 13 % in Nenetses of Tundra, 25 % – in Selkups, and 40 % – in the population of ethnic Russians residing in Siberia [4].

Most of the clinical research shows that the administration of indirect anticoagulants in the carriers of *CYP2C9*2* and *CYP2C9*3* «slow» allelic variants the risk of bleeding goes up 2–3 times, while the risk of excessive hypocoagulation (INR>4) increases 3–4 times. At the same time, of the two «slow» allelic variants only *CYP2C9*3* has an impact on the manifestation of hemorrhagic syndrome [5]. Given the fact that carriers of *CYP2C9*3* allelic variant had a higher decrease in the activity of CYP2C9, it was interesting to look at the distribution of the gene within the study groups. It was found out that the largest number of *CYP2C9*3* «slow» alleles' carriers were among the Armenians (29.0%) and the Karachais (20.0%). Among the Slavs such allelic variant was found only in 12.7% of the cases (8 patients). In assessing the carriage of *CYP2C9*2* prevailing were the Slavs – 25.4%, while the Armenians accounted for 23.7%, and Karachais – only for 5.7%.

Conclusions

1. Higher values of INR against Warfarin intake in the Armenians (compared to the Slavs and the Karachais) coupled with low doses of the drug serve a predictor of a higher risk of bleeding among the Armenians in case of taking Warfarin.

2. High frequency of *CYP2C9*3* allelic variant in Armenians can be a predictor of increased risk of bleeding.

3. The results yielded allow making forecasts, in the populations in question, concerning individual and population-wide risk of adverse response to IDAC. Moreover, there are reasons to expect that Armenians may reveal the maximum level of risk.

4. Since genetic factors determine as much as a half of the adverse effects of medicines, then taking the patient's ethnic affiliation while selecting the appropriate dosage might optimize pharmacotherapy with indirect anticoagulants. Therefore, selection of individual doses of medicinal agents, just like identification of *CYP2C9* genotypes, should be introduced into the list of compulsory medical studies to be performed in clinical practice.

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About authors:

Baturin Vladimir Alexandrovich, Professor, Doctor of Medical Science; Head of Department for Clinical Pharmacology with Course of Post-Graduate and Additional Training, Stavropol State Medical University, Russia;
tel.: +7(8652)713466; e-mail: v_baturin@mail.ru

Tsarukyan Anna Akopovna, Assistant Lecturer; Department for Clinical Pharmacology with Course of Post-Graduate and Additional Training, Stavropol State Medical University, Russia;
tel.: +7(8652)713466; +79054901856; e-mail: a-tsarukyan@mail.ru

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GELATINASE B AND MAGNESIUM IN THE DEVELOPMENT OF EXPERIMENTAL GASTRIC ULCER

Rogova L. N., Shesternina N. V.

Volgograd State Medical University, Volgograd, Russian Federation

РОЛЬ ЖЕЛАТИНАЗЫ В И МАГНИЯ В ФОРМИРОВАНИИ ЭКСПЕРИМЕНТАЛЬНОЙ ЯЗВЫ ЖЕЛУДКА

Л. Н. Рогова, Н. В. Шестернина

Волгоградский государственный медицинский университет, Волгоград, Российская Федерация

Purpose of study was to determine the specific number and expression activity of gelatinase B-positive cells in the ulcerous defect, and the magnesium levels in the concentrated red cells obtained from various locations in rats with experimental acetate gastric ulcer. The experiment was performed on 18 white Wistar rats. The study of the specific number and gelatinase B expression activity was done through immunohistochemistry (Novocastra, NCL–MMP9, for the paraffin blocks, working dilution 1:40); the content of magnesium in red blood cells through the reaction with titan yellow. The study allows concluding that in the site of experimental ulcerous defect there is an increase in the number and the expression activity of gelatinase B-positive cells in the surface epithelium, with even a higher degree of increase in the gastric LPS (cellular component) against lowered magnesium levels in the concentrated red cells.

Key words: experimental acetate gastric ulcer, gelatinase B, magnesium

Цель исследования состояла в изучении удельного числа и активности экспрессии желатиназы В-позитивных клеток в тканях язвенного дефекта и уровня магния в эритроцитарной массе крови из разных регионов у крыс с экспериментальной ацетатной язвой желудка. Эксперименты выполнены на 18 белых крысах линии Вистар. Исследование удельного числа и интенсивности желатиназы В было проведено иммуногистохимическим методом («Novocastra», NCL–MMP9, для парафиновых блоков, рабочее разведение 1:40); содержание магния в эритроцитах – по реакции с титановым желтым. Проведенное исследование позволяет сделать заключение, что в зоне экспериментального язвенного дефекта увеличивается число и интенсивность экспрессии желатиназы В-позитивных клеток в покровном эпителии и еще в большей степени в СПСО (клеточный компонент) на фоне снижения содержания магния в эритроцитарной массе.

Ключевые слова: экспериментальная ацетатная язва желудка, желатиназа В, магний