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POLYMORPHISM OF THE MDR1 GENE IN PATIENTS WITH CHRONIC GASTRITIS

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Resume,

The article discusses the results of genotyping patients to improve the pharmacotherapy of acid-dependent diseases of the digestive system by the CYP2C19 gene, which provides the pharmacokinetics of drugs from the proton pump inhibitor group contributed to improving the effectiveness, safety and personalization of pharmacotherapy, which serves to improve the quality of life of patients.

Keywords: *Genotyping, polymorphism, chronic gastritis, proton pump inhibitors, pharmacotherapy, polymorphic markers.*

Relevance. In the world, one of the most common pathologies among diseases of the gastrointestinal tract is chronic gastritis (HCG). According to the data, 50.8% of the population of developing countries and 34.7% of the population of developed countries suffer from gastritis. The literature describes how its social significance is determined not only by its prevalence, but also by becoming a cause of disability. The importance of chronic gastritis as a serious disease is largely underestimated in clinical practice, although the role of gastritis in the pathogenesis of common peptic ulcers and stomach cancer is obvious. Scientists point out that millions of premature deaths may occur worldwide every year due to cancer and stomach ulcers, which are the consequences of HCG. Complications resulting from the chronic course of the disease and untimely treatment are dangerous to the patient's life, and due to the fact that HCG is a public health problem, its effective treatment is one of the urgent problems of world medical science.

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A number of scientific studies are being conducted all over the world aimed at achieving high efficiency in improving the methods of early detection of HCG, its uncomplicated treatment and prevention of the disease. The main tasks are to conduct a microbiological analysis of patients, the use of effective pharmacotherapeutic agents for microbial eradication, evaluation of the effect of antibacterial drugs on H.pylori and normalization of acid secretion of the stomach. In the treatment of the disease, it is important to pay attention to the genetic characteristics of the patient, analyze their impact on the effectiveness of treatment and, accordingly, improve pharmacotherapy. Although genetic research is an object of fundamental science, modern medicine is difficult to disclose without them. It is known that the basis of an individual response to drugs used in pharmacotherapy is an understanding of the influence of genetic factors. This fact gives doctors and researchers hope for the introduction of modern methods of personification of pharmacotherapy and maximum reduction of the risk of side effects of drugs.

In general, gastritis was more common in men than in women. However, a study conducted in Brazil showed that 67.8% of women and 32.2% of men suffer from chronic gastritis. A systematic review of African countries showed that 38% of women and 18% of men suffer from gastritis. In Kenya, among patients who visited medical institutions, 73.3% of children and 54.8% of adults had a clinical diagnosis of gastritis. Similarly, in Uganda, 44.3% of young people under the age of 12 suffered from gastritis. Finally, as Demissue pointed out in Ethiopia, gastritis is more common in adolescents than in the elderly.

It was found that in Uzbekistan over the past 10 years (2007-2017), the number of patients with gastrointestinal diseases has increased by 22.4%. The annual average increase was 2.65%. A high annual average increase is observed in the city of Tashkent, and a negative increase in the increase in gastrointestinal diseases is observed in the Bukhara region. In the city of Tashkent, the increase in the number of patients is due to the increase in morbidity among children and adolescents, in the Samarkand,

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Tashkent and Syrdarya regions, the increase in the number of patients is observed at the expense of the adult population.

The importance of chronic gastritis as a serious disease is largely underestimated in clinical practice, although the role of gastritis in the pathogenesis of common peptic ulcers and stomach cancer is obvious. It can be estimated that millions of premature deaths may occur worldwide every year due to cancer and ulcers, which are the consequences of chronic gastritis.

The prevalence of chronic gastritis has decreased markedly in developed countries over the past decades. However, chronic gastritis is still one of the most common serious pandemic infections with serious fatal consequences such as stomach ulcers or stomach cancer.

The development of HCG is influenced by etiological factors that are exogenous and endogenous in nature. Particular importance is attached to the etiological role of Helicobacter pylori, since more than 90% of HCG is associated with this infection. In Ethiopia, a systematic review conducted by Marcis et al. It was indicated that 53% of people aged 54 to 61 years suffered from gastritis due to H. Pylori infection. In addition, in Nigeria, 40.7% of children aged 6 to 10 years suffered from gastritis caused by H. Pylori. It was revealed that Uzbekistan belongs to the regions with a high degree of infection of the population with H. Pylori infection – 80%. In this regard, all patients with hCG should include antimicrobial drugs in pharmacotherapy. The purpose of therapy and the success of eradication treatment depends on the effectiveness of the antibacterial drug on H. Pylori, and on the degree of suppression of acid secretion. The drug response is influenced by both clinical factors, such as age, gender, kidney and liver function, concomitant therapy, and genetic factors, the degree of influence of which varies widely for different drugs. Genetic polymorphisms can affect various pharmacological reactions: absorption, distribution, metabolism.

One of the factors determining the effectiveness of antisecretory therapy of HCG is the intensity of metabolism of proton pump inhibitors. At the same time, the genetic factor is a significant source of interindividual differences in the metabolism of drugs.

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The metabolism of drugs of the proton pump inhibitor group is carried out mainly by the enzyme CYP2C19 of the cytochrome P450 superfamily.

The implementation of genetic research has now ceased to be an object of purely fundamental science. Understanding the genetic factors underlying an individual response to a drug gives clinicians hope for the possibility of personalizing therapy and minimizing the risk of side effects. The principles of HCG pharmacotherapy may be standard, but the treatment of the disease cannot be the same for all patients, it must be personalized. This approach is based on the genetic characteristics of the patient.

In modern medicine of our state, a number of measures are being carried out to improve the quality of medical care to the population. The action strategy for the five priority areas of development of the Republic of Uzbekistan in 2017-2021 defines such tasks as "... the introduction of a set of measures to improve and strengthen the health of the population, reduce morbidity, prevent genetic diseases and increase life expectancy ...". The solution of these tasks contributes to the qualified treatment of various diseases, the improvement of methods and approaches to pharmacotherapy using modern technology, identifying the genetic affiliation of each patient for personalized medicine.

The aim of the study is to evaluate the effectiveness of treatment and to determine the possibilities of personal pharmacotherapy by identifying the features of the occurrence of variants of the CYP2C19 gene genotype in patients with chronic gastritis.

Materials and methods of research. A comprehensive examination of 104 patients with chronic gastritis who were on inpatient treatment and observation in the Bukhara regional Medical Center was conducted. The control group consisted of 96 healthy people who had no history of pathology from the digestive tract, living in the Bukhara region, corresponding by gender and age to the examined group of patients with chronic gastritis.

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The age of patients with chronic gastritis ranged from 18 to 67 years. At the same time, it should be noted that women predominated among patients with chronic gastritis.

The initial stage of our work was the selection and optimization of the system of oligoprimes for the detection of polymorphism rs4244285 of the gene SUR2C19 by polymorphic marker G681A. The nucleotide sequences of the rs4244285 polymorphism detection of the SUR2C19 gene were selected using the Oligo v.6.31 program (Molecular Biology Insights Inc., USA) and synthesized at Syntol LLC and NPFLitech" (Moscow).

The remaining components were purchased from the world's leading manufacturers – Serva (Germany), Sigma (USA), Helicon NPFLitech", Sibenzim (Russia), etc.

The adaptation of primer systems for standard PCR analysis was carried out using PCR analyzers "AppliedBiosystems 2720" (USA) and Rotor-Gene 6000 (Corbett Australia). For amplification, a reaction mixture with a volume of 25 µl was used, which contained 2.5 µl of 1 OxTaq buffer (67 mMtris-HCl (pH 8.8), 16.6 mM (NH4)2S04>, 2.5mM MgCl2, 0.01% Tween-20), 0.1 µg of genomic DNA, a mixture of dNTP (dATP, dGTP, dCTP, dTTP of 200 microns each), 1 unit. Termusaquaticus DNA polymerase (manufactured by Silex, Moscow) and 5-10 pM locus-specific oligonucleotide primers. The temperature-time parameters were changed depending on the pairs of oligoprimes.

To detect rs4244285 of the SUR2C19 gene: preliminary denaturation – 940S (1 min. 1 cycle), 35 amplification cycles: 930S (10 sec) – denaturation, 640S (10 sec) – primer annealing, 720S (20 sec) – elongation, and final synthesis 720S (1 min. 1-cycle), 10 min storage.

Polymorphic regions of the SUR2C19 gene were detected using PCR-SSP.

The specificity and number of amplified fragments were checked by electrophoresis in agarose gel.

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Results and their discussion. Individual variability of the drug response is one of the main problems in modern clinical practice [11]. The genetic variability of the genes encoding these enzymes, the patient's genotype plays an important role in the manifestation of individual sensitivity to drugs [12, 23].

Using a modified detection method, we investigated polymorphisms of the MDR-1 gene: polymorphism T3435C of the MDR-1 gene, which has variants of the C/C, T/T, T/S genotypes; polymorphism G2677T of the MDR-1 gene, which has variants of the G/G, T/T, G/T genotypes and polymorphism C1236T of the MDR-1 gene, which has variants of the C/C, T/T, C/T genotypes.

It should be pointed out that, in the structure of the group of patients with chronic gastritis studied by us, living in the Bukhara region, depending on the association with Helicobacter pylori (Figure 1), patients with the polymorphic marker T3435C of the MDR-1 gene had more than 84% of patients with the C/C genotype, and 79% of patients with chronic gastritis, The T/T genotype was associated with Helicobacter pylori and more than 54% of patients were carriers of the heterozygous T/C genotype who had identified chronic gastritis associated with Helicobacter pylori. However, chronic gastritis not associated with Helicobacter pylori in patients with a similar genotype was found in 46% of cases.

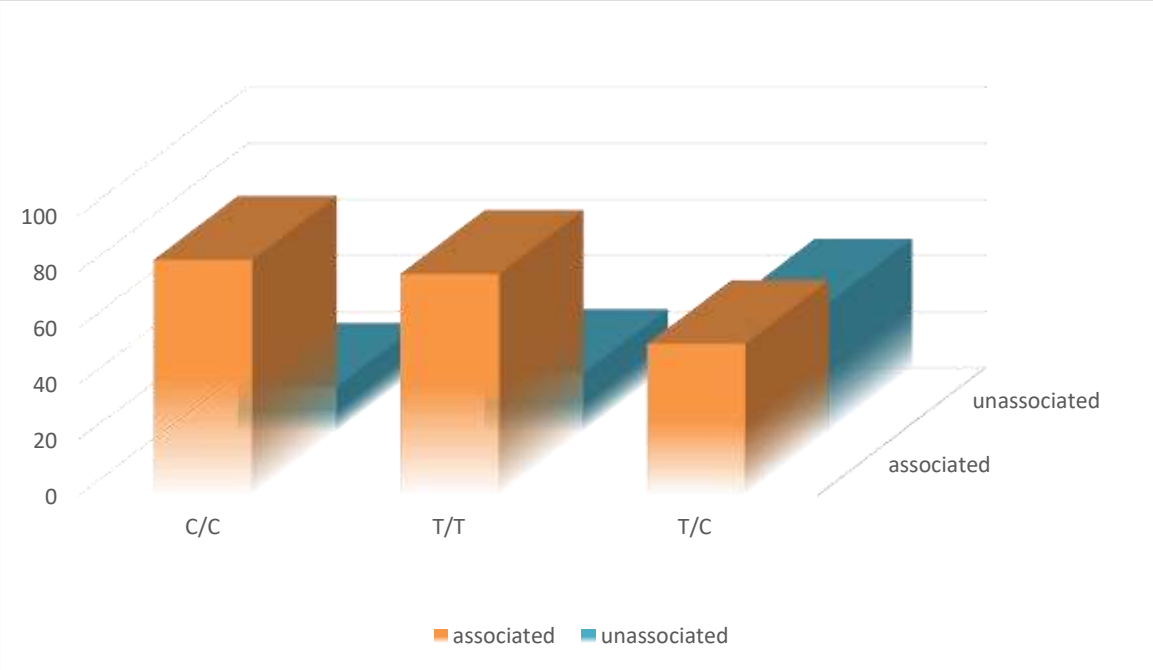

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Figure 1. Frequency of distribution of polymorphism genotypes T3435C MDR-1 gene in chronic gastritis, depending on the association with Helicobacter pylori

Also, when studying the genotypic features of patients with the G2677T polymorphism of the MDR-1 gene (Figure 2), chronic gastritis associated with Helicobacter pylori occurred in 82% of patients with the T/T genotype, and in more than 67% of patients the G/G genotype was detected and patients with the G/T genotype accounted for 56%, in whom chronic gstreet has been associated with Helicobacter pylori. It should be noted that in patients with a similar genotype, chronic gastritis associated with Helicobacter pylori was detected in 44% of cases.

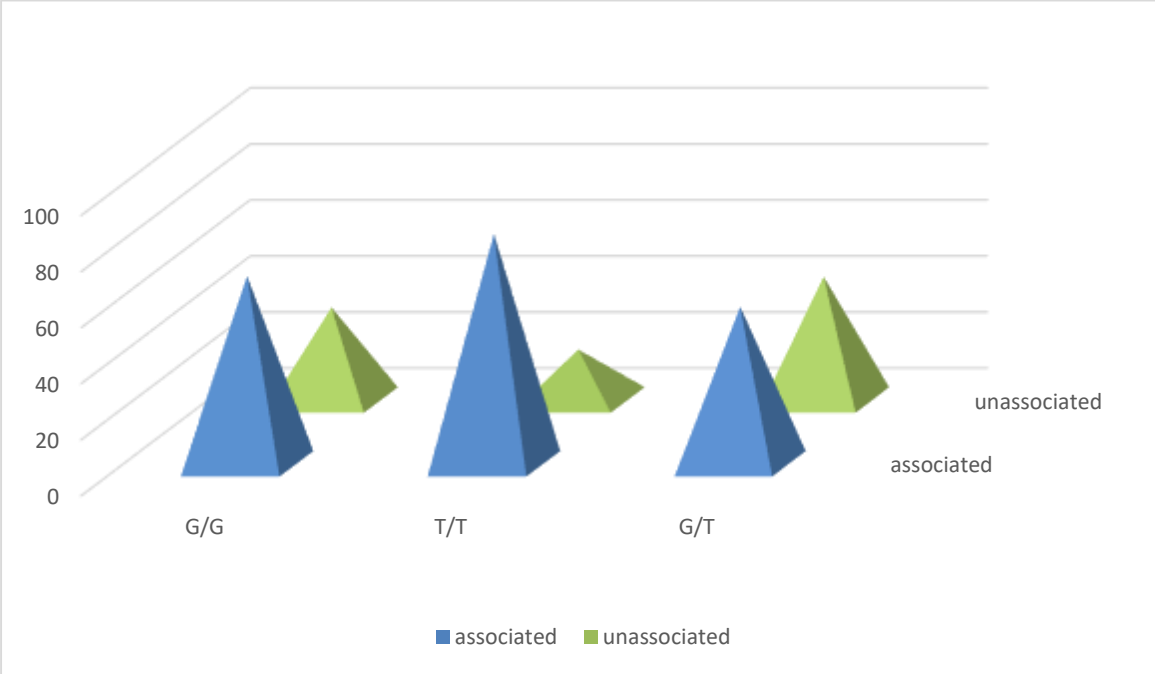

Figure 2. Frequency of distribution of genotypes of polymorphism G2677T MDR-1 gene in chronic gastritis, depending on the association with Helicobacter pylori

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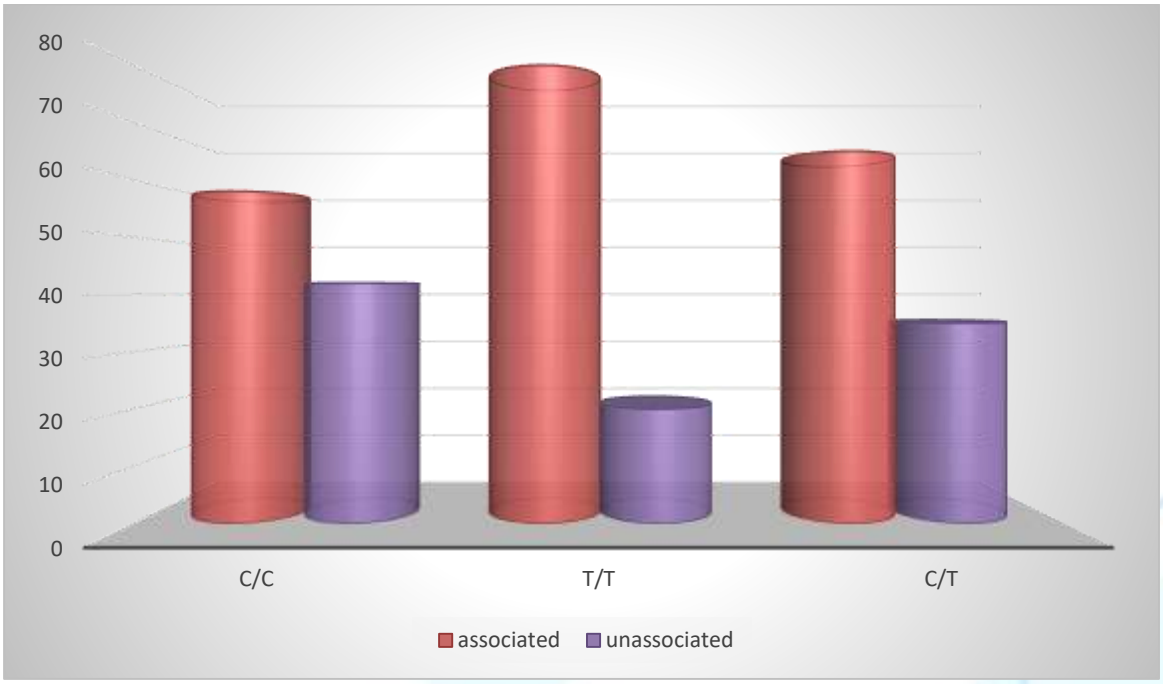

Figure 3. Frequency of distribution of genotypes of polymorphism C1236T of the MDR-1 gene in chronic gastritis, depending on the association with Helicobacter pylori

Chronic gastritis in patients with genotype T/T polymorphism C1236T of the MDR-1 gene (Figure 3) was associated with Helicobacter pylori in 80% of cases, and in patients with genotype C/T of a similar polymorphism of the MDR-1 gene in 65% of cases, the disease was associated with bacterial etiology, whereas in patients with genotype C/T of a similar polymorphism of the MDR-1 gene in 65% of cases, the disease was associated with bacterial etiology, whereas in patients with genotype C/With this indicator was more than 58%. In patients with a similar genotype, in 42% of cases, chronic gastritis was not associated with Helicobacter pylori.

Conclusions

In patients with gastroduodenal pathology, the unfavorable genotype G/A polymorphism rs1800629 of the TNF-α gene is significantly more common compared to conditionally healthy individuals ($p<0.05$).The presence of significant differences indicates the important role of this genotypic variant of the TNF-α gene in the pathogenesis of inflammatory and ulcerative lesions of the gastric mucosa

and duodenum and may contribute to an increased risk of developing HCG and IBD.

The polymorphic variant rs1143634 of the proinflammatory cytokine IL-1ß gene is not independently associated with the formation of chronic gastritis and YABDPC.At the same time, the combination of heterozygous genotypes C/T(IL-1β) + G/A(TNF-α) by OR=2.5 times significantly increases the risk of inflammatory and ulcerative process lesions of the gastric mucosa and duodenum ($\chi 2<3.8$; $P>0.05$).These data prove the hypothesis that the proinflammatory effect of cytokine IL-1ß depends not only on an increase or decrease in the expression of this gene, but also on a combination (syntropic action) with other cytokine genes.

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