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THE KEY TO THE EFFECTIVENESS AND SAFETY OF PHARMACOTHERAPY

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Annotation

The article discusses the issues of genotyping patients with chronic gastritis (CG) for the *2(G681A) polymorphism of the CYP2C19 gene, characterized by the replacement of guanine (G) with adenine (A) at position 681 (rs4244285) in exon 5. The CYP2C19 gene encodes the CYP2C19 isoenzyme, which metabolizes proton pump inhibitors (PPI) - first-line drugs in the pharmacotherapy of CG. The author recommends the choice of drug and its dose depending on the genotypic affiliation of the patient - personification, which ensures the effectiveness and safety of treatment.

Key words: CYP2C19 gene, CYP2C19 G681A polymorphism, chronic gastritis, genotyping, personification

Relevance

A number of scientific studies are being conducted worldwide aimed at achieving high efficiency in improving methods of early detection of chronic gastritis (HCG), its uncomplicated treatment and prevention of the disease [1, 14].

Scientists of Uzbekistan, analyzing statistical information on the republic, indicate that basically 56.6% of diseases of the digestive system are registered in the adult population, and 34.5% in children under the age of 14, which is 8.9% of all gastrointestinal diseases. At the same time, the annual average increase in the incidence of gastrointestinal tract was determined within 2.65%, where the city of Tashkent occupied the leading place, and the Bukhara region occupied the last place in the list of gastrointestinal morbidity. The researchers emphasize the increase in morbidity among the growing generation in the city of Tashkent. It should be noted that in the Samarkand, Tashkent and Syrdarya regions, this indicator increases due to the morbidity of the adult population [3, 8, 13].

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 it. 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

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pharmacotherapy and maximum reduction of the risk of side effects of drugs [6, 9, 17].

In this regard, the main tasks of this direction are an in-depth analysis of the occurrence of genotypes of this gene, the features of the course of diseases depending on the genetic affiliation of the patient, their impact on the results and effectiveness of treatment and, depending on this, the improvement of pharmacotherapy [5, 10, 21].

Cytochrome P-450 enzymes, one of which is CYP2C19, are the main participants in the metabolism of xenobiotics. The genetic variability of the genes encoding these enzymes plays an important role in the manifestation of individual sensitivity to drugs. In modern medicine, a number of scientific studies are conducted to study the effect of the genetic apparatus on the pharmacotherapy of many diseases, on the effectiveness and safety of medicinal products [2, 11, 19].

Proton pump inhibitors (PPIs) play an important role in the short- and long-term treatment of acid-dependent diseases of the digestive system, one of which is HCG [7, 12, 16]. Polymorphic variants of the CYP2C19 gene are involved in their metabolism. Three phenotypes have been identified in different populations: fast, intermediate and slow [4, 15, 18]. Slow metabolizers are characterized by weak drug metabolism because an inactive (defective) enzyme is synthesized [18, 22]. Despite the achievements in this field, scientists recommend investigating the pharmacogenetic parameters of pharmacotherapy, the effects of gene polymorphism, the activity of which provides the pharmacokinetics of drugs, to ensure high efficacy and safety of treatment, which was the purpose of this study.

Materials and methods of research

In addition to clinical, fibrogastroduodenoscopy and other instrumental methods, the research methods included molecular genetic and statistical methods. In the course of molecular genetic studies, biological material for DNA extraction was taken taking into account the established human rights procedure, which was carried out after a medical examination with the written consent of patients (Universal Declaration on the Human Genome and Human Rights (November 11, 1997)).

It is known that one of the variants of the CYP2C19*2 gene (rs4244285) under study consists in replacing guanine (G) with adenine (A) at the 681 (681G-A) position in exon 5. Using a modified detection method, we investigated the polymorphism G681A of the CYP2C19 gene, which has variants of the genotypes A/A, GG, G/A.

Genomic DNA was isolated from whole peripheral venous blood. Blood sampling was performed using a vacuum system containing K2-EDTA as an anticoagulant. DNA isolation was carried out in accordance with the instructions of the DNA/RNA isolation kit (Ribot-prep, Interlabservice, Russia) or according to the Mathew S.S. (1984) method, with some modifications. Real–time PCR amplification was performed. The obtained results were documented in the form of curve growth for two FAM and NEX

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detectors in graphical mode on the corresponding program. Statistical processing of the results of the study was carried out using a generally accepted method using the Student's criterion.

The results of the study

In our studies, 45% of the patients studied were male and 55% female. As indicated by the indicators, women are more likely to suffer from HCG than men. When studying the disease in the age aspect, it was registered more in elderly people (from 40 to 60 years old) and senile (60 years or more) age – 86.25% than in young people (from 15 to 40 years old) – 13,75%.

It should be pointed out that, in the structure of the group studied by us, patients with HCG (Fig. 1), regardless of the type of gastritis, it was revealed that carriers are normal-

The "wild" allele genotype GG(CYP2C19*1/*1) the CYP2C19 (G681A) gene is found in (54) 67.5% containing the "mutant" allele genotype AA(CYP2C19*2/*2) in (2) 2.5%, as well as containing "wild" and "mutant" alleles, the heterozygous genotype GA(CYP2C19*1/*2) occurs in (24) 30% of patients. Thus, the frequency of occurrence of the G allele corresponded to 82%, whereas the frequency of occurrence of the A allele was about 17% in patients with HCG.

It should also be noted that representatives of the control - healthy group have the "wild" allele genotype GG(CYP2C19*1/*1) the CYP2C19 (G681A) gene is found in (16) 80% containing the "wild" and "mutant" allelic heterozygous genotype GA(CYP2C19*1/*2) occurs in (4) 20%, however, containing the "mutant" allele genotype AA (CYP2C19*2/*2) the CYP2C19 gene has not been identified.

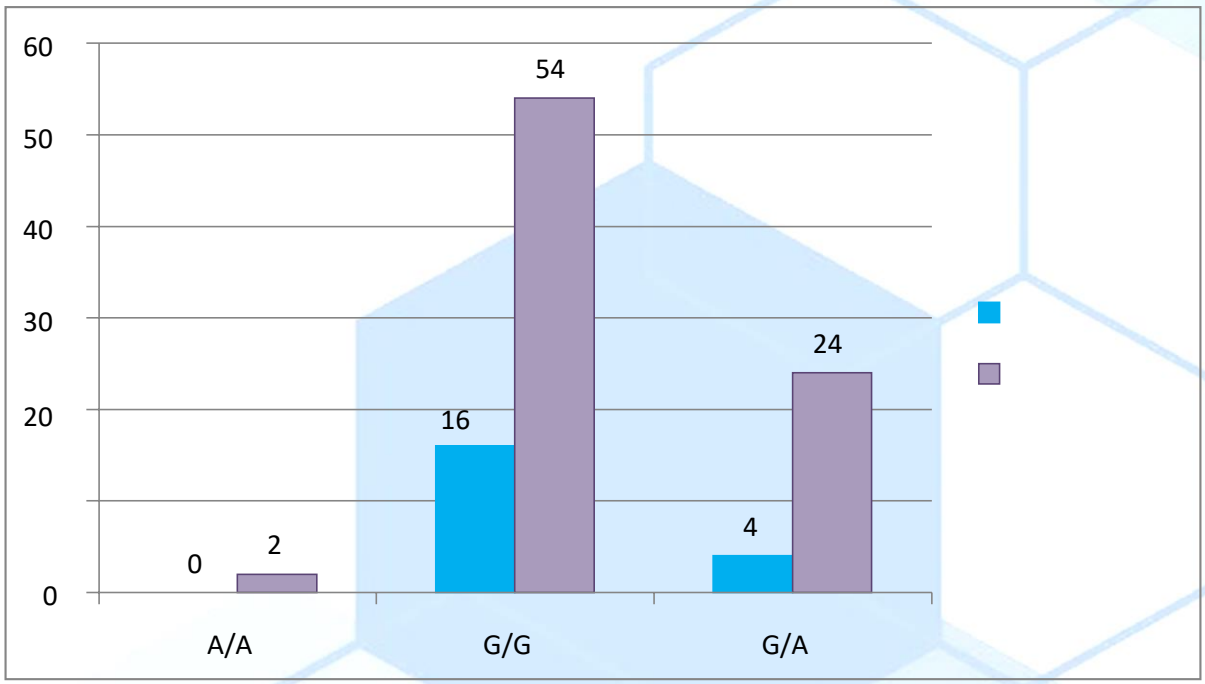

Figure 1. Frequency of genotype distribution according to the G681A allele variant of the SUR2C19 gene

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It is interesting to note that when determining the gender characteristics of HCG, it is 1.5 times more common in women than in men, and also differs in the occurrence of genotypes of the CYP2C19(G681A) gene.

In the selected group of patients with HCG, regardless of the type of disease, the frequency of occurrence of variants of the genotypes of the CYP2C19(G681A) gene was studied by gender division, the results of which showed that the homozygous "wild" allelic genotype GG(CYP2C19*1/*1) the CYP2C19 (G681A) gene is found in more than 66% of women with HCG, whereas in men with a similar diagnosis, this variant of the genotype is 2 times less common (Table 1).

Heterozygous "wild" and "mutant" GA allele genotype(CYP2C19*1/*2) it was detected in more than 62% of women with HCG, but in male patients this variant of the genotype occurs in 37% of cases.

It should be noted that the "mutant" allele genotype AA(CYP2C19*2/*2) among all variants of the CYP2C19 gene genotypes, it is rare – only in women with HCG, and it has not been detected in male patients. The same genotype was not detected in healthy men and women from the control group.

Table 1

Gender characteristics of the frequency of genotype distribution of the G681A allele variant of the CYP2C19 gene in patients with Ce

Variants of genotypes	Study groups							
	Control (n=20)				Experience (n=80)			
	Man		Woman		Man		Woman	
	n	%	n	%	n	%	n	%
A/A	-		-		-		2	100,0
G/G	7	43,75	9	56,25	18	33,33	36	66,67
G/A	2	50,00	2	50,00	9	37,50	15	62,50

In our opinion, the effectiveness of pharmacotherapy of the disease can be influenced by the patient's genotype, especially according to the allele variant G681A, which is often determined in patients with type B HCG (Fig. 2). So, if 50% of patients have the AA genotype containing a "mutant" allele (CYP2C19*2/*2) after pharmacotherapy, recovery from HCG is observed, then the rest of the patients (50%) have pharmacotherapy without improvement.

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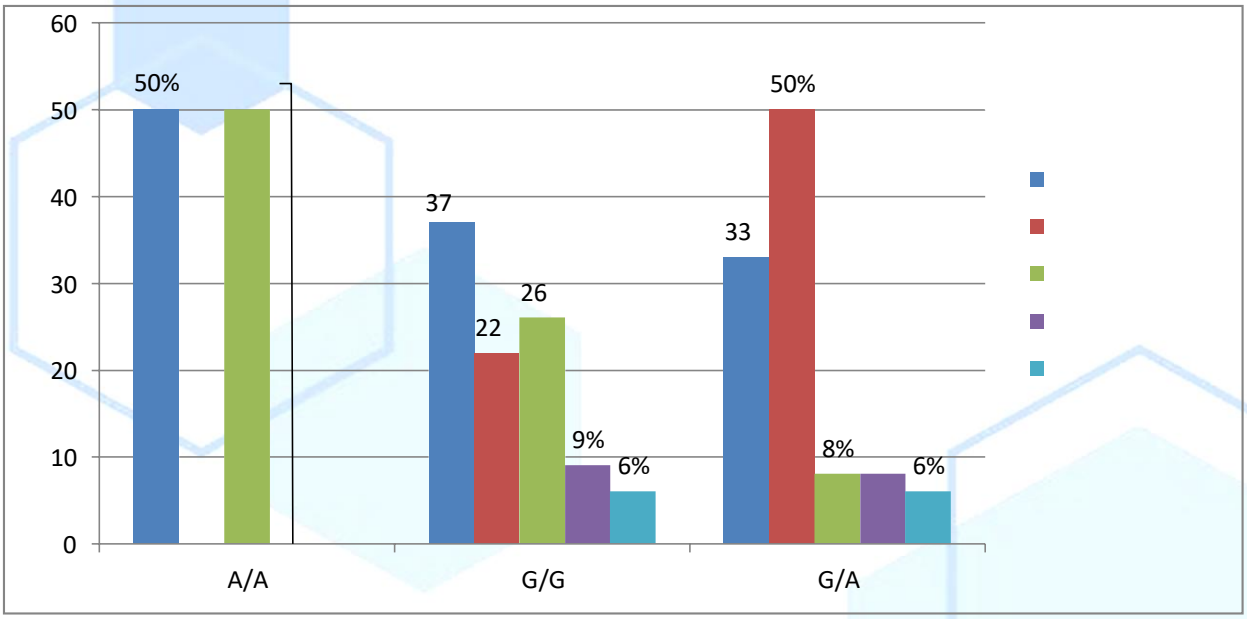

Figure 2. The results of treatment of chronic gastritis and their relationship with the frequency of genotype distribution according to the G681A allele variant of the CYP2C19 gene

Also, 37% of patients with the GG genotype (CYP2C19*1/*1) pharmacotherapy ends with recovery, however, in 22% of patients with a similar genotype, treatment only improves the condition of patients; and in 26% of patients, pharmacotherapy does not have the desired effect – without improvement, and even in 9% of patients with HCG, the condition worsens and complications are observed in 6% of cases.

In addition, patients with heterozygous GA genotype (CYP2C19*1) containing "wild" and "mutant" alleles/*2) recovery was noted in 33%, improvement in 50% of cases, and pharmacotherapy was unsuccessful in 8% of patients and in the same number there were worsenings, complications were noted in 6% of cases.

Thus, adequate efficacy of pharmacotherapy was not observed in the type of chronic gastritis. After this therapy, 1/10 of the patients' condition worsened and 1/20 of the patients had complications of the disease, whereas in patients with heterozygous GA genotype containing "wild" and "mutant" alleles (CYP2C19*1/*2) they were determined more.

Conclusions

The results of the study show that the treatment of He, taking into account the genotypic affiliation of the patient according to the allele variant G681A of the CYP2C19 gene, reveals ways of a differentiated approach and personalization of pharmacotherapy to ensure the effectiveness and safety of pharmacotherapy.

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