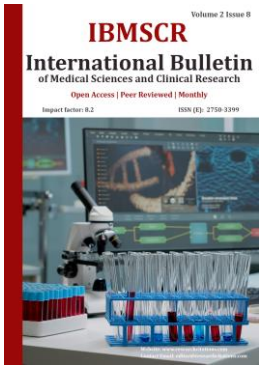

ULCER AND GENETIC MARKERS OF PHARMACOKINETICS: INTERRELATION AND FEATURES

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Resume,
The article reveals the results of a study of the relationship between the genotypes of the CYP2C19 gene in patients with gastric and duodenal ulcers and the manifestation of concomitant diseases. Recommendations are given for the personification of peptic ulcer pharmacotherapy, taking into account genetic markers of pharmacokinetics.
Keywords: Genotypes, peptic ulcer, pharmacotherapy, personification of pharmacotherapy, CYP2C19 gene, G681A and C806T polymorphisms of the CYP2C19 gene, markers of drug pharmacokinetics.

Actuality of the research. A number of scientific studies are being conducted in the world aimed at improving the methods of early detection of diseases of the digestive system, their uncomplicated treatment and prevention, one of which is peptic ulcer disease [5]. The main tasks of the doctor are to conduct a microbiological analysis of patients, the use of effective pharmacotherapeutic agents for microbial eradication, assessment of the effect of antibacterial drugs on H.pylori and normalization of acid secretion of the stomach [17]. 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 [16].

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 [1, 7]. 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 [10, 13].

The principles of peptic ulcer pharmacotherapy may be standard, but the treatment of the disease cannot be the same for all patients, it must be individual, and should be based on the genetic features of the patient [2, 8].

Based on the above, it should be noted that the effectiveness of peptic ulcer pharmacotherapy is directly influenced by the genetic characteristics of the patient, which play an important role as a source of interindividual differences in the metabolic processes of pharmacological substances, especially in the intensive metabolism of drugs of the first line of peptic ulcer pharmacotherapy - proton pump inhibitors, where the main role belongs to the CYP2C19 gene [6, 15].

A number of studies are being conducted in the world aimed at studying the features and influence of polymorphisms of the CYP2C19 gene on the course and effectiveness of treatment of a number of diseases where this gene plays a particularly important role [3, 12].

The activity of this gene determines the pharmacokinetics of a number of drugs, including drugs from the group of proton pump inhibitors, which play a significant role in the treatment of peptic ulcer disease. The occurrence of polymorphic variants among patients determines the effectiveness and safety of the pharmacotherapy used [14, 18]. In this regard, the main objectives of this direction are an in-depth analysis of the occurrence of genotypes of this gene, the peculiarities of the course of diseases depending on the genetic affiliation of the patient, their impact on the results and effectiveness of treatment, on the manifestations of concomitant diseases and, depending on this, the improvement of pharmacotherapy, which was the **purpose** of this study.

MATERIALS AND METHODS OF RESEARCH

A comprehensive examination of 100 patients with peptic ulcer of the stomach and duodenum, who were on inpatient treatment and observation in the Regional Multidisciplinary Clinical Hospital of Bukhara, who made up the observation group, was conducted.

The control group consisted of 20 healthy people who had no history of pathology from the digestive tract, who corresponded by gender and age to the examined group of patients.

The age of patients with peptic ulcer ranged from 18 to 75 years, men were 60 (60%), women – 40 (40%), that is, men significantly prevailed in the sample of patients with peptic ulcer.

In the course of molecular genetic studies, biological material was taken from the venous blood of patients. The collection of material and extraction of genomic DNA from the peripheral blood of patients was carried out considering the established human rights procedure, which was carried out after a medical examination and written consent of the subjects (Universal Declaration on the Human Genome and Human Rights (November 11, 1997)). 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 (Рибо-преп, Интерлабсервис, Russia) or with the methodology, Mathew S. S., 1984, with some modifications. Genotyping of DNA samples by polymorphisms 681 G>A *2 and 806 C>T *17 of the CYP2C19 gene was carried out by real-time PCR using oligonucleotide primers and allele-specific fluorescent probes using a PCR-RV kit (manufactured by «Синтол» LLC (Moscow, Russia)). Real-time PCR amplification was performed using a standard protocol. For real-time PCR amplification, Dtlite4 Real-TimePCR was used. FAM and NEX detectors were introduced into the program. The obtained results were documented in the form of growth curves for two FAM and NEX detectors in graphical mode on the corresponding program.

Statistical processing of the results of the study was carried out by a generally accepted method using the Student's criterion.

RESULTS

It is known that the CYP2C19 gene has several polymorphisms, among which CYP2C19:681 G>A *2 is associated with a decrease in enzyme function and the CYP2C19: 806 C>T *17 polymorphism is associated with increased enzyme function [11, 18]. Polymorphic variant G681A of the gene CYP2C19 is characterized by three genotypes: GG ("wild" type), GA (heterozygous type) and AA ("mutant" type); and polymorphism C806T of this gene has genotypic variants: CC ("wild" type), CT (heterozygous type and TT ("mutant" type).

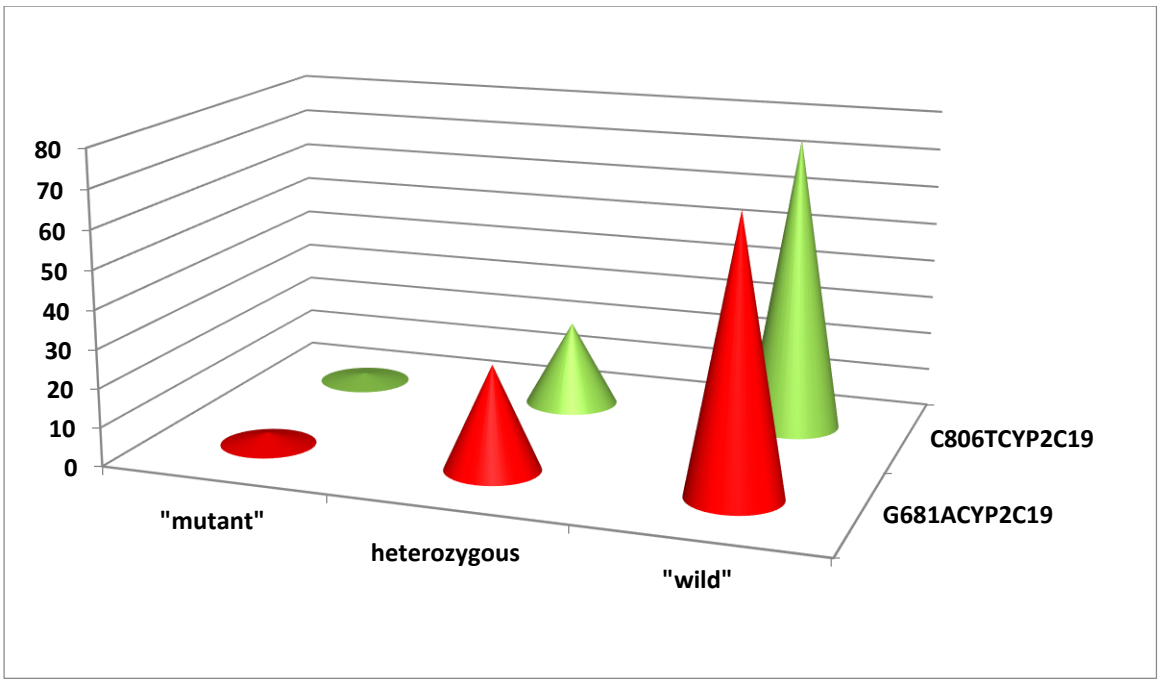

Figure 1. The occurrence of genotypes of polymorphic markers of the CYP2C19 gene among patients with peptic ulcer disease

Thus, when determining the occurrence of genotypes of the studied polymorphisms of the gene CYP2C19 among patients with peptic ulcer disease (Fig. 1), it turned out that among the genotypes of the polymorphic marker G681A, the AA genotype occurs in the smallest number – 3%, and the heterozygous GA genotype in 27% of cases. The TT genotype of the C806T polymorphism of the CYP2C19 gene was detected in 2% of patients, while the heterozygous CT genotype was 22% of patients.

It is assumed that the genotypic affiliation of the patient according to the studied polymorphisms of the gene SUR2C19 have a direct effect on the manifestation of concomitant diseases [4, 9].

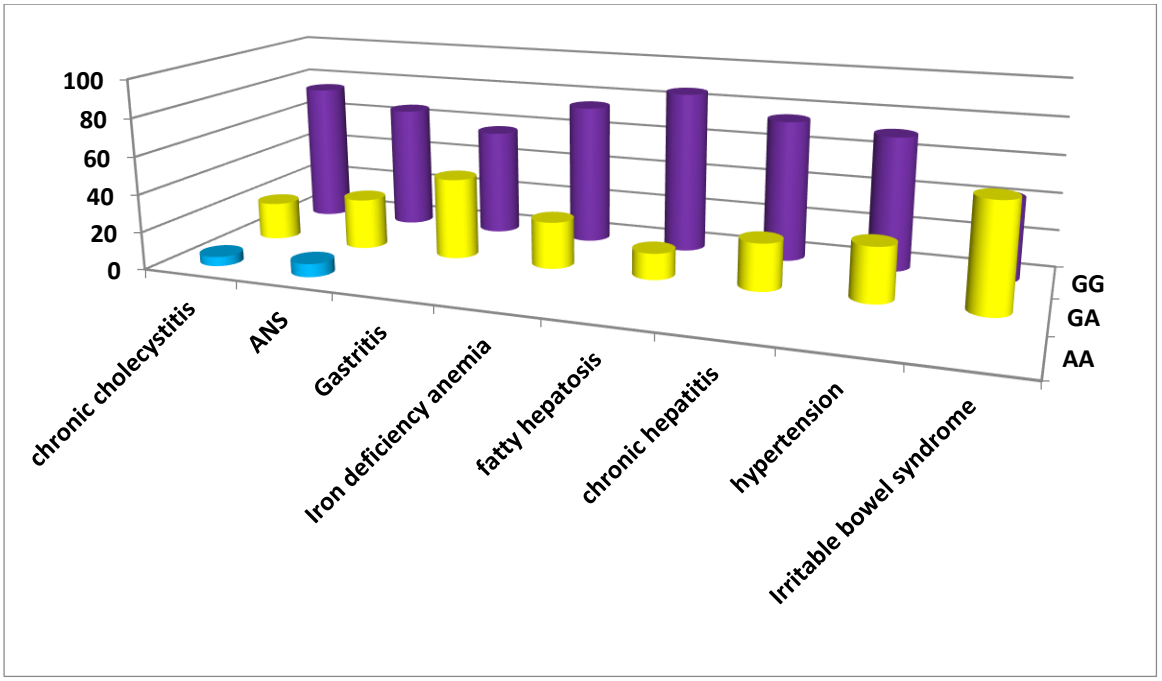

Figure 2. The relationship of concomitant diseases with the patient's genotype of the G681A polymorphism of the CYP2C19 gene

Studies have shown that chronic cholecystitis accompanies peptic ulcer disease more often than other diseases (Fig. 2) and if chronic cholecystitis is detected in 75% of cases in patients with the GG genotype of the polymorphic marker G681A of the CYP2C19 gene, then in 70% of cases it is detected in patients with the CC genotype of the C806T polymorphism of this gene; it should be noted that in the the smallest amount of this nosology was detected in patients with the "mutant" type of the studied polymorphisms of the CYP2C19 gene. The following places are occupied by Asthenic-neurotic syndrome, gastritis, Iron deficiency anemia (IDA), Fatty hepatosis, Chronic hepatitis, Hypertension and Intestinal bowel syndrome (IBS), which are also more often detected in patients with the "wild" type of genotype and in the smallest number in patients with "mutant" genotypic affiliation.

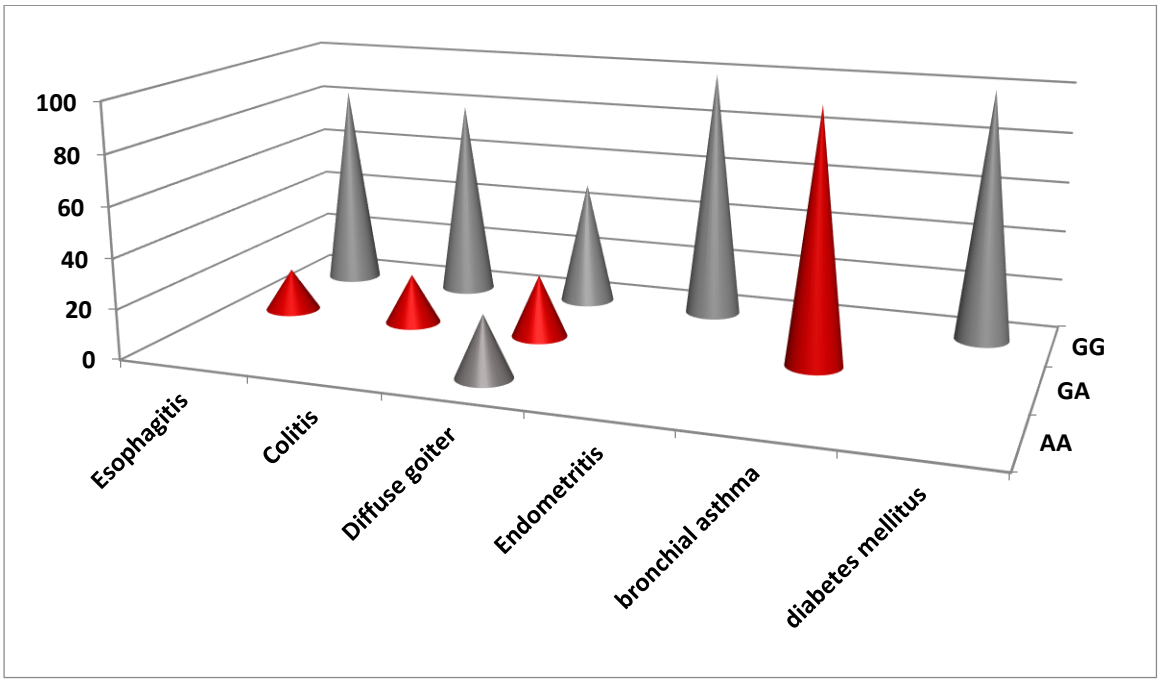

Figure 3. The relationship of concomitant diseases with the patient's genotype of polymorphism C806T of the gene CYP2C19

And such concomitant diseases as Esophagitis, Colitis, Diffuse toxic goiter (Graves disease), Endometritis, Bronchial asthma and Diabetes mellitus were determined in various quantities (Fig. 3) both in patients with heterozygous genotype and in patients with "mutant" genotypic affiliation, but the greatest number were detected in patients with a "wild" genotype.

CONCLUSIONS

Considering the direct influence of polymorphisms of the CYP2C19 gene on the pharmacokinetics of drugs of the first line of peptic ulcer pharmacotherapy – proton pump inhibitors, it is necessary to emphasize their role in the course and treatment of this disease. As can be seen from the results of the study, these genotypes are also important in the development of concomitant diseases, which is quite important for determining the tactics of treatment of peptic ulcer disease.

Thus, it should be noted that the modern approach to the pharmacotherapy of peptic ulcer disease should include the tactics of personification, which is carried out by genotyping the patient, where the main role belongs to the gene CYP2C19.

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