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POLYMORPHISM OF GENES IS FACTOR EFFICIENCY ANTI ULCER PHARMACOTHERAPY

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ABSTRACT

Peptic ulcer disease is one of the variants of the typological response of the body when exogenous factors of the internal environment interact (type of the nervous system, endocrine system, psycho emotional characteristics, metabolism, biochemical reactions, and cytokine profile) with external exogenous factors. This pathology is one of the most common diseases of internal organs, and among the adult population it occurs in 7-12% of cases [1; 2; 3]. Type II stomach ulcers (Johnson H. D., 1965) or combined stomach and duodenal ulcers account for about 25% of the structure of gastric ulcers [7] According to modern research data, up to 10% of residents of Europe, the USA and Russia suffer from this disease (Ivashkin V.T., Minushkin O.N., 2015). In Uzbekistan, about 14% of people develop stomach ulcers; this disease is most common in men. (Https. // nuz.uz Jun 5, 2018) This review article also contains information on the significant effects of gene polymorphisms encoding biotransformation enzymes of drugs on the efficacy and safety of antiulcer pharmacotherapy. Determination of the polymorphism of the CYP3A5 gene makes it possible to initially determine the tactics of treatment with proton pump inhibitors in patients with peptic ulcer disease.

KEYWORDS: *Peptic ulcer disease, the prevalence of Helicobacter pylori disease, Gene polymorphisms pharmacogenetics, Pharmacotherapy.*

INTRODUCTION

Peptic ulcer and duodenal ulcer continue to be one of the most important medical and socio-economic problems of our society. According to WHO, more than 7 million people around the world are registered with diseases of the digestive tract every year and more than one hundred thousand people die from complications of such diseases [4, 5, 6, and 37] In Uzbekistan in 2017,

13.4% of the population had diseases of the gastrointestinal tract, which ranked second among all diseases of the population [10, 11, 12, 35, and 36].

A peptic ulcer is a disease in which an ulcerative defect in the mucous membrane is formed. The disease is observed when the balance between the factors of aggression and protection of the mucous membrane is disturbed. As a result, under the influence of provoking factors, the sub mucosal and muscle layers are affected.

Common causes of peptic ulcer disease are Helicobacter pylori bacteria. In addition, in a large percentage of cases, this disease is caused by non-infectious factors, among which the administration of drugs is leading: non-steroidal anti-inflammatory drugs, antibiotics, glucocorticoids. Also, etiological factors are a person's lifestyle, nervous overstrain, unbalanced diet with insufficient vitamins and excessive consumption of rough, hot, salty and sweet foods, alcohol abuse, smoking and hereditary predisposition. These factors play an important role in the pharmacotherapy of peptic ulcer disease [7, 8, 9, 13, 14, 34, and 35].

Despite the achievements of medical science and the introduction of a huge number of new drugs, the problems of effective and safe pharmacotherapy remain relevant at the present time. Modern pharmacotherapy in most cases includes numerous drugs of synthetic and natural origin [15, 16, 21, 22, 32, and 33]. From the literature it is known that after the introduction of drugs into the body, the place and role of genetic factors is of particular importance in shaping the response of the human body to these drugs: effectiveness, ineffectiveness, and development of adverse side reactions [17, 18, 23, 24, 30, and 31]. The patterns revealed by pharmacogenetics allow the doctor to individually approach the choice of both the drugs themselves and their doses for each individual patient, providing the most effective and safe pharmacotherapy.

As you know, genetic factors or genetic characteristics of a patient are polymorphic regions of genes, the products of which, in one way or another, are involved in the implementation of various pharmacokinetic and pharmaco dynamic processes.

The authors argue that the pharmacokinetic process involves genes encoding biotransformation enzymes and transporters that carry out the absorption, distribution and excretion of drugs from the body. Currently, the role of genes that control the synthesis and work of enzymes of biotransformation of drugs, in particular isoenzymes of cytochrome P-450 (CYP2D6, CYP2C9, CYP2C19, CYP3A5, etc.), enzymes of phase II biotransformation (N-acetyltransferase, glutathione -S-transferase) and drug transporters (P-glycoprotein, transporters of organic anions and cations) [19,20,25,26].

Accordingly, the main task of the pharmacodynamic process is performed by genes encoding target molecules of drugs or proteins (receptors, enzymes, ion channels) functionally linked to these structures. Also included are genes whose products are involved in various pathological processes (blood coagulation factors, apolipoproteins, genes of the HLA system, etc.), against which the corresponding pharmacotherapy is directed [27, 28, and 29].

The main task of modern doctors is to develop and apply in practice the safest and most effective method of treating peptic ulcer disease. However, the selection of quality therapy is still an important problem due to the increased resistance of H. pylori to antibiotic therapy, the widespread use of non-steroidal anti-inflammatory drugs, and other factors [1, 33, and 34].

With the development of pharmacogenetics, it became clear that the potential reasons for the low effectiveness of pharmacotherapy for peptic ulcer disease should be considered in terms of the genetic characteristics of the organism (Makushina A.A. et al., 2017). Pharmacogenetic studies allow predicting the effect of a drug in each patient and selecting an individual effective and safe dose of the drug.

Previous studies have shown that most proton pump inhibitors (proton pump inhibitors) are metabolized by cytochrome CYP2C19, CYP3A4, CYP3A5 enzymes, which are encoded by genes with polymorphism, which determines the pharmacokinetics, pharmacodynamics and drug efficacy [2]. The enzyme CYP2C19 has the greatest effect on the concentration of proton pump inhibitors in plasma [3]. Based on the combinations of CYP2C19 polymorphisms, several phenotypes are distinguished: normal, intermediate, fast and slow metabolizers of proton pump inhibitors [2].

The results of the study revealed a relationship between the genotype of patients according to CYP2C19, the phenotype and the effectiveness of therapy for peptic ulcer disease, which made it possible to develop recommendations for the dosage of drugs [4]. Proton pump inhibitors are also substrates for the P-glycoprotein (P-gp) encoded by the ABCB1 gene. Since P-gp affects the absorption and metabolism of drugs, the ABCB1 gene polymorphism can also affect the success of proton pump inhibitor therapy in patients with peptic ulcer disease. It was found that the carriage of the C3435T polymorphism in the homozygous variant affects the effectiveness of antiulcer and anti-Helicobacter pylori therapy [1, 5].

The CYP3A5 gene encodes the CYP3A5 isoenzyme of cyto chrome P450. The isoenzyme CYP3A5 plays a role in the metabolism of proton pump inhibitors [1]. Studies have shown that the allelic variant of CYP3A5 * 3 (A6986G, rs776746) of the CYP3A5 gene affects the metabolic rate of proton pump inhibitors and, therefore, their pharmacological action [2]. The study of the effect of the carriage of the polymorphic marker CYP3A5 * 3 in patients with peptic ulcer on the effectiveness of proton pump inhibitors may be of clinical importance, since proton pump inhibitors are the first-line drugs of choice in the treatment of peptic ulcer disease[30,31,32,34,35].

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It is known to science that polymorphism of the CYP2C19 gene in different ethnic groups for everyone - in Europeans if it is 2-5%, and in Asians these indicators are different: in Koreans, 12%, in the population of the Southwest Pacific, 70%. If the metabolism of inhibitors in the G / G genotype for the CYP2C19 gene is enhanced, and in the G / A genotype, drug metabolism is weaker and this is of particular importance for the effective and safe use of drugs.

Science knows that polymorphism of the CYP2S19 gene is different for different ethnic groups - in Europeans 2-5%, in Asians it is different, for example, in Koreans 12%, in the peoples of the Southwest Pacific 70% []. While the metabolism of inhibitors the proton pump in the G / G

genotype according to CYP2S19 is accelerated, the metabolism of drugs in the G / A genotype is reduced, which is important for the effective and safe use of drugs.

According to the literature, in patients with chronic gastritis in the Bukhara region, the G / G genotype for this gene is 79%, which indicates an accelerated metabolism of proton pump inhibitors, which should be taken into account when dosing drugs. A high frequency of CYP2C19 * 17, CYP3A5 * polymorphisms was found. 3, as well as rs1045642 and rs4148738 ABCB1 among patients with gastric ulcer and duodenal ulcer. Further studies of the effect of these polymorphisms on the effectiveness of therapy with proton pump inhibitors in patients with gastric ulcer and duodenal ulcer are required.

A high prevalence of CYP3A5 * 3 polymorphism was found among patients with gastric ulcer and duodenal ulcer. Further study of the role of this polymorphism in the metabolism of proton pump inhibitors is required.

CONCLUSION

It is quite possible that in the near future the knowledge that each patient who is a carrier of a certain genotype and allele of pepsinogen, pepsin, hydrochloric acid, hormones, gastrin, components-factors of immune inflammation, pro- and anti-inflammatory cytokines and others, which, when studied on large samples of patients will show the impact on the development of peptic ulcer disease, as well as the widespread creation of a genetic passport for the entire population will allow us to predict the development of the disease with a certain degree of probability in each individual.

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