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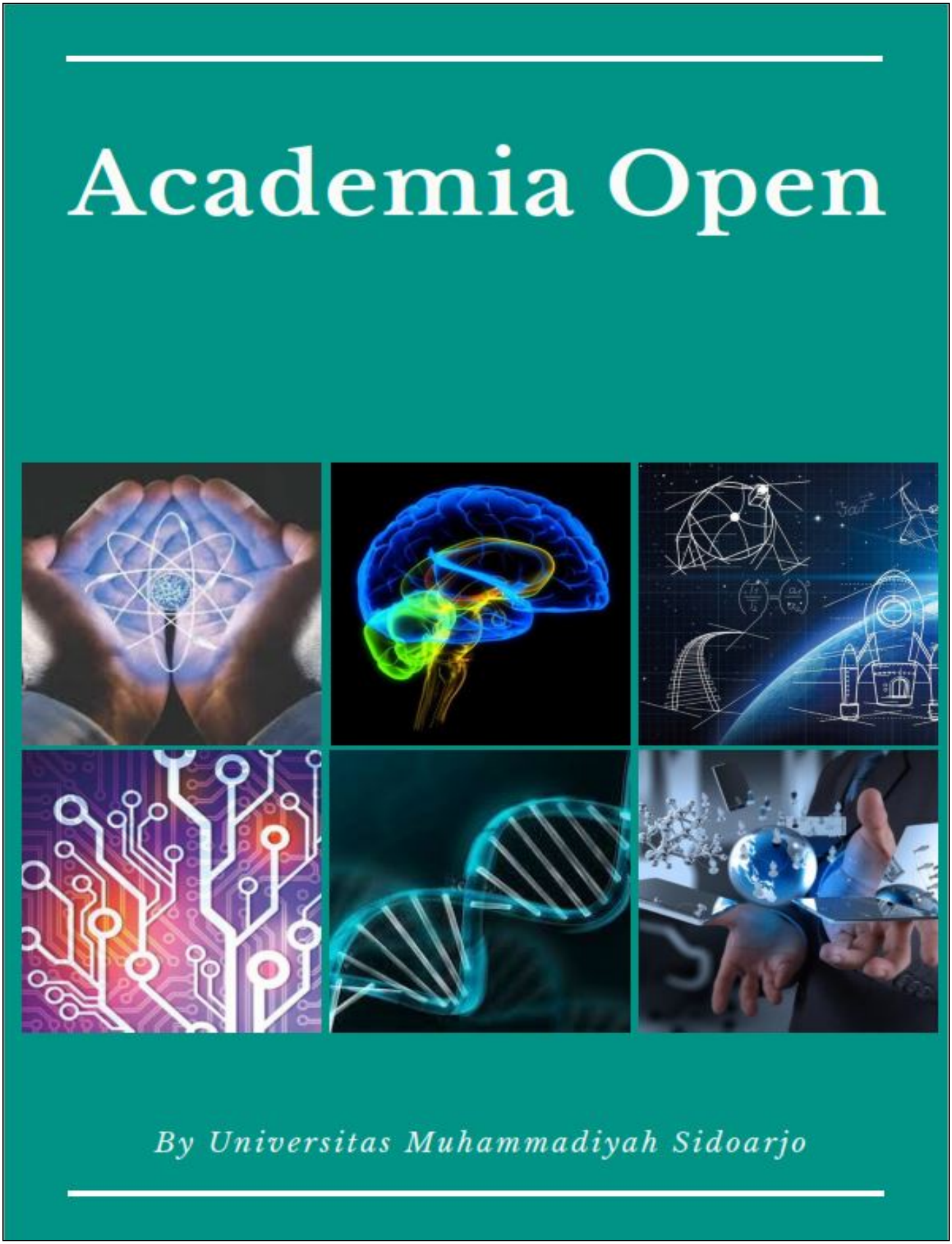

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Efficacy and Safety of Pharmacotherapy of Chronic Gastritis

Khasiat dan Keamanan Farmakoterapi Gastritis Kronis

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Abstract

The MDR-1 gene encodes P-glycoprotein, a vital membrane protein found in various normal cells throughout the body. This protein plays a crucial role in actively facilitating the absorption of drugs across cell membranes. Understanding the expression of P-glycoprotein is essential for comprehending drug pharmacokinetics and optimizing pharmacotherapy outcomes. In this study, our goal was to investigate the influence of P-glycoprotein expression on drug permeability and its implications for therapeutic effectiveness. Through a comprehensive analysis of existing literature, we explored the methods employed to assess P-glycoprotein activity and its impact on drug absorption. The results unveiled the pivotal role of P-glycoprotein in modulating drug permeability and highlighted its significance in determining pharmacotherapy outcomes. This research emphasizes the necessity of considering P-glycoprotein expression when designing drug delivery strategies, enabling targeted therapies, and maximizing therapeutic efficacy.

Highlights:

- P-glycoprotein: Key regulator of drug permeability and cellular absorption.
- Influence of P-glycoprotein expression on pharmacotherapy outcomes.
- Importance of considering P-glycoprotein in drug delivery and targeted therapies.

Keywords: MDR-1 gene, P-glycoprotein, drug permeability, pharmacokinetics, pharmacotherapy effectiveness.

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Introduction

The study of the genetic differences of patients for the selection of drugs in order to increase the effectiveness of pharmacotherapy in medicine has managed to acquire paramount importance[1, 5,]. Because the genetic characteristics of the patient serve the variability and difference of the body's response to a particular drug of pharmacotherapy [3, 4, 12]. It should be mentioned that the genetic component is one of the main factors influencing the pharmacological response. This is also indicated by statistical data, according to which up to 60% of the variability of the body's response to the effects of drugs is associated with genetic variations of a patient with a particular disease [6, 9, 14]. Accordingly, the recommended introduction of the use of information about the genetic characteristics of the patient in clinical practice will allow in all areas of medicine to develop protocols for pharmacotherapy of diseases, new methods of monitoring patients, as well as reduce the risk of adverse reactions, prevent them and maximize the effectiveness, ensure the safety of pharmacotherapy. [11, 13].

It is known that the effect of drugs in the body is directly related to its therapeutic concentration, which must be created not only in the blood, but also in target cells [2, 5, 10]. The MDR1 gene (multidrug-resistance gene) is a gene of multidrug resistance, is the main gene regulating the creation of the necessary intracellular concentration of drugs [4, 8, 15]. The MDR1 gene promotes cell binding to drugs, its entry into the cell, and/or efflux into the intercellular space [9, 10], which explains the development of cell resistance to drugs during the expression of this gene. Therefore, the MDR1 gene plays an important role in the effectiveness of pharmacotherapy of various diseases, including HG [7, 10, 12].

Such regulation of pharmacokinetic processes is often the same for many groups of drugs [4, 9], regardless of the location and form of influence, the main of which may be enzymes of the cytochrome P450 family [11] and such transport proteins as - glycoprotein P (P-gp) - the most important representative of the ABC transporter superfamily (ATP-binding cassette, subfamily B), an ATP-binding cassette protein of subfamily B involved in drug transfer [2, 4, 9].

The high–molecular membrane protein - Pgp is located in the cytoplasmic membrane of cells of many organs and tissues of the body and, in the form of an ATP-dependent pump, promotes the efflux of xenobiotics into the intercellular space [13], thereby protecting the cell from the effects of xenobiotics [3, 7, 10], which is the main function of Pgp. This protein, located in the cell membrane, prevents the absorption of drugs in the intestine; prevents the penetration of drugs through histohematic barriers, in addition, the excretion of drugs into the bile by the liver and urine by the kidneys [6, 15]. The Pgp protein has been detected in the membrane of many organs and tissues of the body: in the liver, it is located on the surface of liver cells and it is contained by small biliary ducts of the liver on its apical surface; also found on the same surface of enteral epithelial cells and colon cells; also, in the kidneys, it is located on the membrane of proximal tubules and found on the apical surface pancreatic small ducts [2, 6].

Under the influence of many drugs, the activity of the Pgp protein can be modulated [12, 11]. Thus, drugs can inhibit the functional activity of the transporter protein or become inducers of Pgp. It is known that inhibitor drugs reduce the functional activity of the Ddr protein and often cause the development of HP [5, 13]. In this group of medicines by Marolim S. And his co-authors, (2004) include such drugs as quinidine, verapamil, carvedilol, spironolactone, as well as many antifungal drugs. It should be noted that in parallel, in this case, the concentration of drugs that are substrates of the Pgp protein increases in the body, due to an increase in absorption and slowing down the excretion of these drugs, the risk of HP increases [3, 8]. There are a lot of such drugs -substrates of the Pgp protein, they include drugs: digoxin, diltiazem, erythromycin, levofloxacin and others. But among all these groups of drugs, PPIs and clarithromycin, which are the main drugs of eradication therapy in H. pylori-associated HG, are of particular importance for the pharmacotherapy of HG.

Some drugs are inducers of Pgp, which increase the functional activity of the transporter protein, thereby simultaneously contributing to a decrease in the concentration in the blood plasma of drugs that are substrates of the Pgp protein, since Pgp at the same time inhibits the absorption of drugs and accelerates their excretion, resulting in a decrease in the effectiveness of drugs. According to Sadeque J.M. and his co-authors (2000), St. John's wort extracts, rifampicin and other drugs are considered to be Pgp protein inducers [5, 9, 16].

The purpose of the study the analysis of types, clinical manifestations of chronic gastritis according to genotypic variants of polymorphism C3435T, G2677T and C1236T of the gene (MDR-1) transporter of xenobiotics glycoprotein P, as well as pharmacoepidemiological evaluation of the treatment process.

Methods

The age of patients with chronic gastritis ranged from 18 to 63 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

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polymorphism rs1045642 of the MDR-1 gene by polymorphic marker C3435T and polymorphism rs4244285 of the CYP2C19 gene by polymorphic marker G681A, i.e. improvements in the methodological method for detecting these genetic markers. Nucleotide sequences of detection of polymorphism rs1045642 of the MDR-1 gene and polymorphism rs4244285 of the CYP2C19 gene were selected using the program "Oligo v.6.31" (Molecular Biology Insights Inc., USA) and synthesized in "Syntol" and "Litech" (Moscow).

Results

In our studies, we also determined the effect of polymorphisms C3435T, G2677T, C1236T of the MDR1 gene on the effectiveness of pharmacotherapy of HG associated with H.pylori. The results of pharmacotherapy were evaluated by the criteria of recovery, improvement, no improvement, deterioration and complications.

It is known that the polymorphism C3435T of the MDR1 gene has genotypes C/S, T/Thousand/T. After the pharmacotherapy, the following treatment results were noted depending on the genotype: in patients with the C/C genotype, recovery, without improvement, deterioration and complications were noted in the same amounts and were 15% each, but improvement was noted in about 39% of patients with a similar genotype (Fig. 1).

Figure 1. *The results of H G treatment and their relationship with the frequency of distribution of C3435T polymorphism genotypes of the MDR1 gene*

It turned out that in patients with the T/T genotype, pharmacotherapy ended in recovery and improvement in 31 and 49% of cases, but in 21% of patients, treatment was without improvement, nevertheless, in patients with a similar genotype, no deterioration and complications were noted. Patients with the C/T genotype accounted for the main number of patients and recovery occurred in about 40% of cases, but patients with and without improvement after pharmacotherapy accounted for the same number – about 29%; 9% of patients had deterioration and 2% of patients suffered from complications.

In addition, polymorphisms G2677T, C1236T of the MDR1 gene were studied. Polymorphism G2677T has genotypes G/G, TT and G/T. The results of treatment were evaluated according to the same criteria. Thus, in patients with genotypic affiliation G/G, recovery occurred in about 39% of patients, while improvements were noted in 33% of cases, 22% of patients were without improvement, deterioration was detected in about 6% of patients, but complications were not detected (Fig.2).

Figure 2. *The results of H G treatment and their relationship with the frequency of distribution of genotypes of the G2677T polymorphism of the MDR1 gene*

In patients with the T/T genotype, treatment had a high effect and recovery was noted in 31% of patients, the condition of 37.5% of patients also improved, but without improvement or even deterioration were in 25% and 6% of patients, respectively, no complications were noted.

Heterozygous genotype G/T was detected more than other genotypes of the studied polymorphism and pharmacotherapy ended with recovery in about 38% of patients, improvement was found in 24% of patients, without improvement were about 18% of patients, while deterioration was noted in 13% of cases and complications were observed in 6.66% of patients.

Polymorphism C1236T of the MDR1 gene has genotypes C/C, T/T housand/T. Like the previous polymorphisms, the genotypes of this polymorphic variant of the studied gene were distributed according to the criteria for evaluating the results of pharmacotherapy. So, if pharmacotherapy showed good results in patients with the C/C genotype and 35% of patients had recovery from the disease and 29% of patients had improvement, then 17% of patients had no improvement, and 11% had deterioration and about 6% of patients had complications (Fig.3).

Figure 3. *Results of treatment of He and their relationship with the frequency of distribution of genotypes of polymorphism C1236T of the MDR1 gene*

Patients with the T/T genotype recovered in 45.5% of cases and the condition improved in 27%, but 18% of patients were without improvement and deterioration was observed in 9% of patients, but there were no complications.

Patients with genotypic affiliation with / T made up a huge part of the studied and the results according to the criteria for evaluating pharmacotherapy were as follows: recovery occurred in about 33% of patients, improvement after treatment was in about 29% of patients, but 21% of patients were without improvement, while deterioration and complications were detected in 13 and about 4% patients, respectively.

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Conclusions

Thus, the research results show that in order to obtain a complete pharmacotherapeutic effect, the doctor needs to have information about the patient's genotype. Such patient data helps the doctor to optimize the chosen treatment plan and, most importantly, to select the dose and treat the patient effectively and safely.

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