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OPTIMIZATION OF PHARMACOTHERAPY BASED ON RESEARCH OF DRUG BIOTRANSFORMATION

Tashenova Asia Imanbekona,
Associate Professor,
Department of Clinical Pharmacology. Kazakh-Russian
Medical University (KRMU), Almaty, Kazakhstan
Tazhimetov Bekzat Makhmutovich,
Senior Lecturer at the Department of Pathological Anatomy and Forensic medicine. KRMU, Almaty, Kazakhstan
Baytemirova Tazhigul Azizovna,
Senior Lecturer at the Department of Clinical Pharmacology
KRMU, Almaty, Kazakhstan
Esirgepova Sofia Richardovna
Head of the Department of Pathological Anatomy
forensic medicine. KRMU, Almaty, Kazakhstan

Abstract: *:studies show that one of the main causes of interindividual and intraindividual variations in the concentration of drugs when taken in standard doses is the change in the rate of biotransformation of drugs and the activity of transporters.*

Key words*: biotransformation system, medicines*

Relevance of the work. Thanks to the achievements of clinical medicine and the introduction of many new drugs (drugs), carefully studied from the point of view of evidence-based medicine, the issues of effective and safe pharmacotherapy remain relevant today. In addition, the effectiveness of pharmacotherapy remains insufficient: on average, drug treatment is effective in only 40% of patients. Today, a complex question has arisen that requires an urgent solution: why in some patients the concentration of drugs in a standard dose (according to the instructions) was at a toxic level, and in others at a low therapeutic level, which naturally caused the development of adverse reactions to the drug in the first case, and in the second category of patients there was no pharmacological effect. It has been established that one of the ways to increase the effectiveness and safety of pharmacotherapy is the introduction of so-called technologies into clinical practice. personalized medicine.

The functioning of the biotransformation system and transporters is a major factor determining the therapeutic level of drug concentration in the human body, and changes in the activity of this system can ultimately lead to an “inadequate response” to the drug when used in standard doses. From this point of view, the development of technologies that allow optimizing drug therapy for each person based on studying the biotransformation and activity of transporters seems promising. And the introduction of this approach into clinical practice helps to increase the effectiveness and safety of drug therapy. Results of the work Academician of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor V.G. Kukes in this area contributed to the creation of this article.

The goal of the work is to develop methods for optimizing drug therapy for the most common and socially significant human diseases based on studying the biotransformation system and the activity of drug transporters. Based on the goal, the following tasks were formulated:

1. Development of accessible and reproducible methods for assessing the activity of the main biotransformation enzymes (CYP3A4, CYP2D6, CYP2C9) and glycoprotein P-drug transporter.

2. Study the mechanisms of drug interaction at the level of the biotransformation system and transporters by assessing the effect of drug inhibitors and inducers on the activity of CYP3A4, CYP2D6, CYP2C9 and glycoprotein-P.

3. Study of changes in the activity of CYP3A4, CYP2D6, CYP2C9 and glycoprotein-P in severe diseases.

4. Assessing the significance of pharmacogenetic studies of CYP3A4, CYP2D6, CYP2C9 and P-glycoprotein for individualizing drug therapy.

5. Development and implementation of algorithms for personalization of drug therapy based on studying the activity of the main biotransformation enzymes (CYP3A4, CYP2D6, CYP2C9) and glycoprotein P-drug transporter. The set goals were fully achieved by conducting clinical studies in conditions close to real clinical practice.

CYP3A4 is the most important drug biotransformation enzyme, as it metabolizes more than 50% of all drugs used in clinical practice, for example, cardiac drugs (calcium channel blockers, antiarrhythmic drugs, aldosterone antagonists, statins), antiallergic, anticancer drugs. etc. b. A method for assessing CYP3A4 activity has been developed. Determination of the concentration of lidocaine metabolite MEGX in blood plasma by high-performance liquid chromatography 30 minutes after a single intravenous administration of lidocaine is called -. MEGX test. Standards were derived from MEGX testing. In addition, the results of the MEGX test revealed differences in CYP3A4 activity depending on the time of day: CYP3A4 activity was higher in the evening than in the morning. On this basis, it is recommended to take into account biorhythms when prescribing drugs that are CYP ZA4 substrates. The effects of inhibitor drugs (antifungals such as fluconazole) and inducer drugs (carbamazepine) on CYP3A4 activity were examined using the MEGX assay. Fluconazole has been shown to reduce CYP3A4 activity, while carbamazepine increases it. Clinical consequences are shown in patients with arterial hypertension receiving slow calcium channel blockers, and in patients suffering from other diseases (fungus and trigeminal neuralgia, respectively). In patients with arterial hypertension, when combined with fluconazole and fungal diseases, an increase in the concentration of verapamil and nifedipine was observed, which was accompanied by an increased risk of adverse reactions in the form of arterial hypotension, bradycardia and atrioventricular block.

On the other hand, the addition of carbamazepine in combination with trigeminal neuralgia in patients with arterial hypertension leads to a decrease in the concentration of verapamil and nifedipine, which is accompanied by a decrease in their effectiveness in the form of an increase in blood pressure. Similarly in patients with hyperlipidemia II A and II B. The addition of fluconazole to treatment with lovastatin increases its concentration, as well as its active metabolite, which is accompanied by an increased risk of complications from striated muscles. In addition, it was found that the maximum inhibitory and inductive effect develops after 5-7 days, and the elimination of the inhibitory or inductive effect also occurs after 5-7

days. Based on this, algorithms for dose adjustment of drugs metabolized by CYP3A4, including drug inhibitors or inducers, have been developed. The effect of diseases on CYP3A4 activity, assessed using the MEGX test, was studied. We found that in patients with decompensated chronic heart failure (CHF), CYP3A4 activity, as measured by the MEGX test, is very low. We showed that decompensated CHF has low concentrations of the active metabolite of spironolactone conrenone due to low CYP3A4 activity and at the same time high concentrations of aldosterone. Based on this, it was concluded that for effective treatment of secondary hyperaldosteronism in patients with decompensated heart failure, an increase in CYP3A4 activity, observed with the use of loop diuretics and low doses (5-10 mg per day), is necessary.) glucocorticoids. We also found decreased CYP3A4 activity in patients with cirrhosis, sepsis, and asthma exacerbations. Based on this, algorithms have been developed for selecting dosage regimens for drugs metabolized by CYP3A4 in patients with liver cirrhosis, sepsis and exacerbation of bronchial asthma.

Conclusion

Research suggests that one of the main causes of interindividual and interindividual variations in drug concentrations when administered at a standard dose is changes in the rate of drug biotransformation and transporter activity. It has been established that these processes can be influenced by three factors: polymorphism of the corresponding genes, induction or inhibition of these systems under the influence of drugs, and the presence of diseases of internal organs. Based on the data obtained, the need to improve the requirements for the examination of new drugs is justified: it has been proven that new drugs are subject to registration only if the manufacturer of the new drugs provides data on the biotransformation of the drug and its transporters, as well as on the biotransformation of drugs. According to the results of these studies, the use of algorithms for personalizing drug therapy in clinical practice can reduce the frequency of adverse reactions by an average of 3 times, increase the effectiveness of drugs by an average of 50%, reduce hospitalization time by an average of 25%, and also reduce overall direct and indirect costs.

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