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Clinical Pharmacology Of Metabolism-Activating And Correcting Drugs

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Abstract. The article covers the issues of drug metabolism in patients with various liver diseases, presents pathophysiological mechanisms of impaired biotransformation of substances depending on the severity of hepatocyte damage, names the causes of drug interactions of pharmacological agents, leading to an undesirable increase in the concentration of the drug in the blood, strengthening and prolongation of the therapeutic effect with an increased risk of side effects.
Keywords: therapeutic action, biotransformation of substances, metabolism.

INTRODUCTION

Metabolism (biotransformation) is a complex of physical and biochemical changes that drugs (LS) undergo in the liver to reduce solubility in fats and change biological activity, during which polar water-soluble substances (metabolites) are formed and excreted from the body [1–3]. As a result of biotransformation of drugs, the following occurs:

inactivation of drugs with a decrease in their pharmacological activity;

increase in the activity of drugs;

formation of toxic metabolites.

Most drugs are soluble in lipids, easily penetrate biological membranes and quickly reach target tissue, but are unable to be eliminated from the body. The transformation of these drugs occurs with the formation of water-soluble metabolites, which are excreted from the body with bile and urine [2].

A pharmacologically active drug can be transformed into another active substance, while the metabolites of some drugs can be less active and less toxic than the original compounds. Biotransformation of other drugs leads to the formation of metabolites that are more active compared to the drugs introduced into the body [3].

There are two types of chemical reactions of drug metabolism in the body:

The underlying synthetic reactions are conjugation of drugs with endogenous substrates (glucuronic, acetic, sulfuric acid, adenosylmethionine, sulfates, glycine, glutathione, methyl groups and water). The connection of these substances with drugs occurs through functional groups: hydroxyl, carboxyl, amine, epoxy. After the reaction is complete, the drug molecule becomes more polar and is more easily excreted from the body [4].

In non-synthetic transformations, drug molecules with initially pharmacological activity change by oxidation, reduction and hydrolysis towards a decrease, increase or complete loss of activity.

MATERIALS AND METHODS

Non-synthetic reactions of drug metabolism are divided into two groups: non-microsomal and microsomal. Non-microsomal enzymes biotransform a small number of drugs in the liver by conjugation (excluding glucuronide), reduction and hydrolysis. Most microsomal biotransformation processes occur in the liver by oxidation, reduction and hydrolysis reactions [1]. Oxidation is the process of adding an oxygen atom to a drug molecule and/or removing a hydrogen atom. Reduction is the process of adding a hydrogen atom to a drug molecule and/or removing an oxygen atom. Hydrolysis is the process of adding water [2]. Microsomal transformation is performed by fat-soluble drugs that penetrate the membranes of the endoplasmic reticulum of hepatocytes and bind to cytochromes [3]. There are two phases of drug metabolism. In the first phase of metabolism, hydroxylation, oxidation, reduction or hydrolysis occurs with the participation of enzymes. A chemically active radical appears in the molecule, to which a conjugating molecule is attached in the second phase [4]. The P450 hemoprotein system is located in the microsomal fraction of hepatocytes - the smooth

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endoplasmic reticulum. It includes monooxygenases, cytochrome C reductase, cytochrome P450 [5]. Cytochrome P450 activates molecular oxygen and the oxidized substrate, changing their electronic structure and facilitating the hydroxylation process. The enzymatic activity of the hepatocyte depends on previous therapy for existing liver diseases and genetics, which explains the hepatotoxic selective effect in some patients. Depending on the intense or weak activity of enzymes, drug metabolism occurs. The main liver enzyme is cytochrome CYP3A4, it makes up 60% of the total number of cytochromes, metabolizes 60% of drugs and is responsible for the induction or inhibition of microsomal enzymes [2]. Drugs metabolized by CYP2D6 have a narrow therapeutic index, i.e. there is little difference between the dose required to achieve a therapeutic effect and the toxic dose. An increase in the drug concentration may cause toxic effects, while a decrease may cause a loss of effectiveness.

RESULTS AND DISCUSSION

In the second phase of biotransformation, drugs or their metabolites combine with one water-soluble molecule (glutathione, sulfate, glucuronides), losing their biological activity. As a result, water-soluble conjugates are formed, which are eliminated by the kidneys or, if their relative molecular weight exceeds 200 kDa, with bile.

Glucuronic acid, formed from glucose, is an important conjugating substance soluble in water. Conjugation of substances with glucuronic acid leads to the formation of polar compounds that are less toxic compared to the original unconjugated products of the first stage. Congenital deficiency of bilirubin conjugate formation causes hyperbilirubinemia with increased levels of unconjugated bilirubin (Gilbert's syndrome). Benign functional familial unconjugated hyperbilirubinemia is characterized by increased serum bilirubin levels (21–85 μmol/L) [3]. The disease is caused by a defect in the gene in the second pair of chromosomes encoding uridine diphosphate glucuronyl transferase, a microsomal enzyme that converts unconjugated bilirubin into conjugated mono- and diglucuronide bilirubin. This defect is inherited in an autosomal recessive manner [5]. In Gilbert's syndrome, the binding of bilirubin to glucuronic acid in the liver is reduced to 30% of the norm [4]. Morphological examination of the liver does not reveal any pathological changes except for lipofuscinosis. Lipofuscin is a glycoprotein, a product of lipid oxidation and, partially, proteins that accumulate due to a deficiency of microsomal enzymes. Small granules are found in the liver in hepatocytes near the central veins. A test with phenobarbital, which induces conjugating uridine diphosphate glucuronyl transferase of the liver, causes a decrease in the bilirubin level. In patients with Gilbert's syndrome, the metabolism of drugs metabolized by microsomal enzymes (cytochrome P-450) is altered.

The activity of many enzymes responsible for drug metabolism is affected by other drugs. When two active drugs compete for one binding site on an enzyme, the metabolism of the drug with less activity slows down and its duration of action increases [2]. There are drugs that can change the action of enzymes responsible for drug metabolism, causing rapid or slow inactivation of other drugs. An increase in enzyme activity is called induction, and a decrease is called inhibition. During induction, a drug stimulates the synthesis or reduces the destruction of enzymes involved in the metabolism of another drug. Substances that induce enzymes are soluble in fats and serve as substrates for the enzymes they induce. Drugs that increase the activity of cytochrome P450 are called stimulants. As a result of the action of stimulants, the rate of metabolism of both the drug itself that caused the induction of the enzyme and other drugs metabolized with its participation increases. These processes lead to a decrease in the serum concentration of the drug, weakening the severity and duration of action. If active or toxic metabolites are formed during metabolism, the therapeutic and side effects, on the contrary, increase.

Enzyme induction is characterized by an increase in their quantity and activity, which is accompanied by hypertrophy of the endoplasmic reticulum of liver cells, in which metabolizing enzymes are localized. Sudden cancellation or cessation of the inductor leads to an increase in the plasma concentration of the drug, which was previously intensively metabolized. In Gilbert's syndrome, jaundice can be leveled out using inducers. Long-term use of the drug leads to the induction of its metabolizing enzymes, as a result of which the metabolism of the drug increases by 2-4 times.

The speed of development and reversibility of enzyme induction depends on the inductor and the rate of synthesis of new enzymes. This adaptation process is slow and takes from several days to several months. Inhibition of drug metabolism enzymes is the cause of drug interactions, which leads to an undesirable increase in the concentration of the drug in the blood, strengthening and prolonging the therapeutic effect

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with an increased risk of side effects. At the same time, the serum concentration of metabolites decreases. This occurs when two drugs compete for a bond with one enzyme. While P450 enzymes metabolize the first drug, the second drug may lose the ability to be metabolized and accumulate in excess in the body.

CONCLUSION

The clearance of these drugs in the absence of liver disease depends on the intensity of hepatic blood flow and the characteristics of metabolic transformations. Normally, after passage through the liver of an orally administered drug of this group, its concentration in the blood of the hepatic vein is an insignificant percentage of the concentration in the portal vein, i.e. already at this stage, a significant part of the drug is metabolized. The presence of portosystemic and intrahepatic shunting contributes to a decrease in drug extraction, as a result of which a significant part of the drug from the gastrointestinal tract enters the general bloodstream, bypassing the liver. With a decrease in hepatic blood flow and a decrease in the metabolizing capacity of the liver, the concentration of the drug in the plasma increases. Thus, with a decrease in the excretion of the drug by the liver from 95 to 90%, its concentration in the plasma increases by 2 times. The second group of substances is drugs with low hepatic extraction. With a decrease in the metabolic capabilities of the hepatocyte to 70%, the content of drugs of this group in the blood increases after the introduction of a single dose, therefore the risk of overdose is small, but metabolic failure with long-term administration of drugs of this group causes their cumulation. Hepatic clearance of drugs of the second group depends on the capacity of the enzymatic systems of the liver. If all enzymes are involved in the metabolism of the drug due to its very large dose, the metabolic rate becomes maximum and does not depend on the concentration in the blood and the dose of the drug, then this is zero-order kinetics. With first-order kinetics, the rate of drug metabolism is directly proportional to its concentration in the blood, when a small part of the metabolizing enzymes is involved in the process. As the concentration of drugs in the blood decreases, the kinetics can change from zero to first order. Thus, the metabolism of drugs metabolized by microsomal enzymes (cytochrome P-450) depends on the liver diseases the patient has, and the degree of biotransformation impairment depends on the severity of the hepatocyte damage. Due to the slowdown in elimination, the therapeutic and side effects of the drug are enhanced.

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