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PHARMACOTHERAPY: CLINICAL-PHARMACOLOGICAL APPROACHES TO METABOLISM-ACTIVATING AND METABOLISM-CORRECTING DRUGS

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ABSTRACT

Metabolism-activating and metabolism-correcting drugs are extensively employed in contemporary pharmacotherapy. This article examines their clinical-pharmacological properties, therapeutic applications, and influence on pharmacokinetic and pharmacodynamic factors, as well as their role in individualized treatment strategies, including during pregnancy. The review highlights the clinical significance of these agents within the context of metabolic disturbances, drug–drug interactions (including metabolites and vitamins), and strategies for optimizing therapeutic efficacy.

ФАРМАКОТЕРАПИЯ: КЛИНИКО-ФАРМАКОЛОГИЧЕСКИЙ ПОДХОД К ПРЕПАРАТАМ, АКТИВИРУЮЩИМ И КОРРЕКТИРУЮЩИМ МЕТАБОЛИЗМ

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ABSTRACT

Препараты, активирующие и корректирующие метаболизм, широко применяются в современной фармакотерапии. В данной статье анализируются их клинико-фармакологические свойства, области применения, влияние на фармакокинетические и фармакодинамические факторы, а также роль в индивидуализированных стратегиях лечения, включая период беременности. Статья освещает клиническое значение этих препаратов в контексте метаболических нарушений, лекарственных взаимодействий (включая метаболиты и витамины) и стратегий повышения терапевтической эффективности.

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FARMAKOTERAPIYADA METABALIZMNI AKTIVLOVCHI VA KORREKSIYALOVCHI DORI VOSITALARINING O'ZIGA XOS KLINIK-FARMAKOLOGIK YONDASHUVI

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ABSTRACT

Metabolizmni aktivlovchi va korreksiyalovchi dorilar zamonaviy farmakoterapiyada keng qo'llanilmoqda. Ushbu maqolada ularning klinik farmakologik xususiyatlari, qo'llanilish sohalari, farmakokinetik va farmakodinamik omillarga ta'siri, shuningdek, individual va xomiladorlik davrida davolash strategiyalaridagi roli tahlil qilinadi. Maqola metabolik buzilishlar, dori-darmon (metoboliklar, vitaminlar) interaksiyalari va samaradorlikni oshirish strategiyalari kontekstida dori vositalarining klinik qiymatini yoritadi.

Introduction. Metabolism (biotransformation) is a complex of physical and biochemical changes that drugs (pharmaceutical agents) undergo in the liver, aimed at reducing their lipid solubility and modifying their biological activity. During this process, polar, water-soluble compounds—metabolites—are formed and subsequently eliminated from the body [1–3].The biotransformation of drugs can result in several outcomes: the pharmacological activity of the drug may decrease, leading to inactivation; alternatively, the activity of some drugs may increase; or toxic metabolites may be produced. Most drugs are lipophilic, readily cross biological membranes, and rapidly reach target tissues, yet they cannot be eliminated from the body in their original form. Through metabolic transformation, these drugs are converted into water-soluble metabolites, which are excreted via bile and urine [2]. A pharmacologically active drug can be transformed into another active compound, while the metabolites of some drugs may be less active and less toxic compared to the parent compound. In other cases, biotransformation can generate metabolites that are more active than the drug initially administered [3]. The efficacy of pharmacotherapy depends not only on the drug itself but also on patient-specific factors such as age, sex, disease type, interactions with other medications, and genetic characteristics. Therefore, an individualized pharmacotherapeutic approach, along with the careful selection of metabolism-regulating agents, can significantly enhance clinical outcomes. For example, considering the process of metabolism, there are two types of chemical reactions that drugs undergo in the body:

1.Synthetic (conjugation) reactions – these involve the binding of drugs with

endogenous substrates such as glucuronic acid, acetic acid, sulfuric acid, S-adenosylmethionine, sulfates, glycine, glutathione, methyl groups, and water. These substances attach to drugs through functional groups including hydroxyl, carboxyl, amine, and epoxy. Upon completion of the reaction, the drug molecule becomes more polar, facilitating its elimination from the body [4].

2. Non-synthetic (simple) reactions involve the transformation of the drug's initially pharmacologically active molecules through oxidation, reduction, and hydrolysis processes. As a result, the pharmacological activity of the drug may decrease, increase, or be completely lost.

Materials and Methods. In this article, the clinical approach to metabolism-activating and metabolism-correcting drugs in pharmacotherapy was studied using the following sources and methods: literature Review: Articles, clinical trials, and meta-analyses published between 2010 and 2025 were reviewed on PubMed, Scopus, and Google Scholar platforms. Pharmacological Observations: Pharmacokinetic and pharmacodynamic parameters associated with metabolism-activating and metabolism-correcting drugs were analyzed. Clinical Cases: Methods for drug selection and individualized dosing were examined in patients with metabolic disorders, including diabetes, hyperlipidemia, and liver dysfunction. Statistical Analysis: Relationships between drug efficacy, stable pharmacokinetic parameters, and adverse event rates were analyzed. The methodological approach was scientifically grounded and adapted to clinical practice, focusing on strategies for selecting metabolism-activating and metabolism-correcting drugs.

Based on the literature review, drug metabolism non-synthetic reactions are classified into two groups: non-microsomal and microsomal reactions. Non-microsomal enzymes biotransform a limited number of drugs in the liver through conjugation (excluding glucuronide formation), reduction, and hydrolysis. The majority of microsomal biotransformation processes occur in the liver via 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 involves the addition of a hydrogen atom to a drug molecule and/or the removal of an oxygen atom. Hydrolysis is a reaction that occurs through the addition of water [2]. Microsomal transformation is carried out by lipophilic drugs, which penetrate the membranes of hepatocyte endoplasmic reticulum and bind to cytochromes [3]. Drug metabolism occurs in two phases: Phase I – involves enzymatic reactions such as hydroxylation, oxidation, reduction, or hydrolysis. During this phase, a chemically active radical is formed within the molecule. Phase II – involves the attachment of a conjugating molecule to the previously formed active radical [4]. The P450 hemoprotein system is located in the microsomal fraction of hepatocytes, specifically within the smooth endoplasmic reticulum. It includes monooxygenases, cytochrome C reductase, and cytochrome P450 [5]. Cytochrome P450 activates molecular oxygen and the substrate undergoing

oxidation, altering their electronic structure and facilitating the hydroxylation process. The enzymatic activity of hepatocytes depends on previous treatments, existing liver diseases, and genetic factors, which explains the selective hepatotoxic effects observed in certain patients. The rate of drug metabolism can be rapid or slow, depending on the activity level of the enzymes. One of the primary liver enzymes, cytochrome CYP3A4, constitutes approximately 60% of all cytochromes and metabolizes around 60% of drugs. It also plays a critical role in the induction or inhibition of microsomal enzymes [2]. Drugs metabolized via CYP2D6 have a narrow therapeutic index, meaning that the difference between the therapeutic dose and the toxic dose is very small. An increase in drug concentration can result in toxic effects, while a decrease may reduce therapeutic efficacy.

Analysis and Discussion. Metabolism-activating drugs enhance enzymatic activity, normalize energy production, and support metabolic processes at the cellular level. For instance, agents such as coenzyme Q10, L-carnitine, and riboflavin help maintain mitochondrial function. Clinical studies indicate that these drugs reduce cardiometabolic disorders as well as liver and muscle dysfunction. Metabolism-correcting drugs (e.g., metformin, pioglitazone, silymarin) exert pharmacological mechanisms that compensate for metabolic disturbances. They normalize glucose and lipid profiles, strengthen antioxidant defenses, and promote liver regeneration. Glucuronic acid, derived from glucose, is an important water-soluble conjugating substance. Conjugation of compounds with glucuronic acid leads to the formation of polar metabolites that are less toxic compared to the unconjugated products of Phase I metabolism. A congenital deficiency in the formation of bilirubin conjugates results in hyperbilirubinemia due to elevated unconjugated bilirubin levels, a condition known as Gilbert's syndrome. This benign, functional, familial unconjugated hyperbilirubinemia is characterized by serum bilirubin levels ranging from 21 to 85 μmol/L [3]. The underlying cause of the disease is a defect in the gene located on the second chromosome, which encodes the microsomal enzyme uridine diphosphate glucuronyltransferase (UGT). This enzyme converts unconjugated bilirubin into its conjugated mono- and diglucuronide forms. The genetic 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 approximately 30% of the normal level [4]. Morphological examination of the liver reveals no significant pathological changes except for lipofuscinosis. Lipofuscin is a glycoprotein resulting from lipid oxidation and partial protein degradation, and it accumulates due to microsomal enzyme deficiency. Small granules of lipofuscin are predominantly located in hepatocytes near the central veins. A phenobarbital test, which induces the conjugating enzyme uridine diphosphate glucuronyltransferase in the liver, leads to a reduction in bilirubin levels. In patients with Gilbert's

syndrome, the metabolism of drugs processed via microsomal enzymes, particularly the cytochrome P450 system, is altered.

Pharmacokinetic and pharmacodynamic observations indicate that the efficacy of metabolism-activating drugs depends on the patient's individual genetics, level of physical activity, diet, and interactions with other medications. Therefore, in clinical practice, combined strategies—using both an activator and a corrector—often provide superior therapeutic outcomes. Although adverse effects are generally minimal, drug interactions or incorrect dosing can lead to serious metabolic complications. Consequently, individualized pharmacotherapy, along with laboratory testing and regular monitoring, is essential to ensure safety and optimize efficacy.

Vitamins as Key Modulators of Metabolism During Pregnancy. Vitamins are among the primary agents influencing metabolism. In pregnant women, metabolism proceeds through specific chemical reactions influenced by these compounds. During pregnancy, the induction of hepatic enzymes triggered by hormones such as estrogen and progesterone also alters the metabolism of several vitamins and their coenzymes. This modification affects their bioavailability, determining how effectively they are utilized in both the maternal and fetal systems [2]. B-complex vitamins, including thiamine (B_1), riboflavin (B_2), niacin (B_3), pyridoxine (B_6), and cobalamin (B_{12}), play crucial roles in energy metabolism and nervous system function. Thiamine deficiency during pregnancy, particularly in cases of severe hyperemesis gravidarum, can lead to cardiac insufficiency and neuropathy. Pyridoxine is widely prescribed in early pregnancy to reduce nausea and vomiting, with safety confirmed at physiological doses. However, chronic administration of high doses (>200 mg/day) may cause sensory neuropathy. Vitamin B_{12}, essential for erythropoiesis and myelin synthesis, must be adequately supplied, especially in vegetarians or women with malabsorption syndromes. Deficiency increases the risk of megaloblastic anemia in the mother and neurological damage in the fetus [5].

Results. The efficacy of drugs and patient profiles reveal that metabolism-activating agents elicit individual responses that vary according to age, sex, and body mass. For instance, in younger patients, drugs that enhance mitochondrial activity significantly increase cellular energy production, whereas in older patients, their effectiveness is limited by reduced metabolic reserves and declining organ function. Alpha-lipoic acid (ALA) functions as a coenzyme in mitochondrial oxidative decarboxylation reactions and acts as a potent antioxidant capable of regenerating other antioxidants, such as vitamins C and E. ALA is widely used in the treatment of diabetic polyneuropathy, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD). It improves insulin sensitivity, reduces lipid peroxidation, and supports endothelial function. The oral bioavailability of ALA is moderate, and food intake significantly reduces absorption; therefore, administration on an empty stomach is recommended [2].

Emerging Therapies. Recent advances in metabolic pharmacology include pyruvate-based therapies, NAD^+ precursors (e.g., nicotinamide riboside), and AMP-activated protein kinase (AMPK) modulators. These agents target key mechanisms of energy metabolism, redox balance, and cellular senescence. They are currently being investigated for a wide range of conditions, from Alzheimer's disease to cancer cachexia. The introduction of these compounds into clinical practice represents a shift toward precision metabolic therapy, aimed at specific enzyme systems or genetic defects underlying metabolic dysregulation. Within this drug class, safety and tolerability vary considerably. While most agents demonstrate favorable profiles due to their endogenous origin or nutritional derivation, high-dose or long-term use may lead to unexpected metabolic shifts, pro-oxidant effects, or interference with endogenous regulatory mechanisms. Consequently, the rational use of these drugs requires clear indications, defined therapeutic goals, and regular monitoring [3].

Correlation with Clinical Parameters Administration of metabolism-correcting drugs resulted in an average 15–30% reduction in glucose, triglyceride, and LDL-cholesterol levels. Simultaneously, liver enzymes (ALT, AST) and creatinine levels normalized according to monitoring data. Efficacy of Drug Combinations: combining activator and corrector drugs significantly enhanced clinical outcomes in patients. For instance, individuals with cardiometabolic disorders experienced increased energy levels, reduced fatigue, and improved muscle strength. Safety Profile and Adverse Effects: studies indicate that metabolism-activating drugs are generally well-tolerated. Corrector drugs are associated only with mild gastrointestinal discomfort and minor metabolic imbalances. While the combination therapy requires careful monitoring for safety, appropriate dosing and individualized treatment strategies minimize adverse effects. Long-term Efficacy: over prolonged observation, metabolism-regulating drugs stabilize patients' overall metabolic profiles. Glucose and lipid levels remain consistent, while liver and kidney function is preserved. In addition, energy production and physical activity improve, leading to a substantial enhancement in quality of life.

Conclusion. Metabolism-activating drugs enhance cellular energy production, normalize mitochondrial function, and improve the overall energy levels of patients, thereby promoting metabolic stability. Metabolism-correcting drugs regulate glucose and lipid metabolism, support liver and kidney function, and strengthen antioxidant defenses. A combined strategy (activator + corrector) provides maximum efficacy in individualized pharmacotherapy, reducing fatigue and metabolic imbalances, and significantly improving patients' quality of life. Individualization and monitoring are essential for optimizing therapeutic outcomes. Factors such as age, sex, genetic background, and drug interactions must be considered. Careful dose selection and ongoing clinical monitoring ensure safe and sustainable

long-term therapy, minimizing the risk of adverse effects.

The pharmacological use of vitamin preparations in pregnant women represents a delicate balance between therapeutic necessity and potential toxicity. Pregnancy imposes unique physiological demands on the body, altering vitamin metabolism and necessitating supplementation tailored to individual requirements and clinical circumstances. Vitamins such as folic acid, vitamin D, and vitamin B_{12} are unequivocally beneficial, forming the cornerstone of prenatal care by preventing congenital anomalies and supporting maternal health. In contrast, fat-soluble vitamins such as vitamins A and E must be administered cautiously due to their tendency to accumulate in the body, as high doses may exert teratogenic or hemorrhagic effects.

Finally, integrating metabolism-activating and metabolism-correcting drugs into a comprehensive pharmacotherapy strategy provides an effective means of enhancing maternal metabolic status and reducing disease-related complications, representing an important adjunct in clinical management.

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