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CLINICAL PHARMACOLOGY OF HYPOGLYCEMIC DRUGS

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Abstract: Current drugs for the treatment of type 2 diabetes mellitus have different molecular targets and different mechanisms of action. The use of these drugs in the form of monotherapy and combination therapy makes it possible to achieve reliable disease control. However, the rational choice of a pharmacotherapy strategy for type 2 diabetes mellitus is a difficult problem in clinical practice. The article discusses some aspects of this problem.

Key words: type 2 diabetes mellitus, glycemic control, choice of pharmacotherapy strategy

Diabetes mellitus (DM) is defined by the World Health Organization as the only chronic non-communicable disease. The pandemic rate of growth of the disease in December 2006 prompted the United Nations to adopt a resolution calling for "the establishment of national programs for the prevention, treatment and prevention of diabetes and its complications and their inclusion in public health programs".

This determines the intensity of ongoing scientific research both in the field of fundamental theoretical knowledge and in the field of clinical application of existing knowledge. The arsenal of practicing doctors is constantly being replenished with new effective drugs, which, given the existing diversity, makes it relevant to consider clinical and pharmacological approaches to the selection and use of various drugs for the pharmacotherapy of diabetes mellitus, since the selection of adequate glucose-lowering therapy and the necessary degree of compensation for carbohydrate metabolism presents certain difficulties.

Currently, on the entire planet, based on the number of patients treated, there are more than 250 million patients with diabetes mellitus, and about 50% of all patients with diabetes are in the most active, working age of 40-59 years. Considering the growth rate of the prevalence of this disease, experts from the International Diabetes Federation (IDF) predict that the number of people with diabetes will increase by 1.5 times by 2025 and reach 380 million people, mainly due to patients with type 2 diabetes (T2DM), which is developing in adults and is causally associated, first of all, with excess body weight (IDF atlas, 2009). High rates of growth in the incidence of diabetes, especially type 2 diabetes, continue in the Russian Federation. Over the past 10 years, the number of patients with diabetes in terms of visits has doubled and reached more than 3 million people. Meanwhile, data from control and epidemiological studies conducted by the Endocrine Research Center from 2002 to 2008 showed that the real number of patients is 2-3 times higher and amounts to about 9 million people.

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According to etiology, pathogenesis and clinical manifestations, diabetes mellitus is usually divided into two types. Type 1 diabetes (T1D) is caused by autoimmune or idiopathic destruction of pancreatic beta cells, usually leading to absolute insulin deficiency. The triggering mechanism for type 2 diabetes is the functional inferiority of the β-cell against the background of severe insulin resistance.

The most dangerous consequences of the global epidemic of diabetes mellitus are its systemic vascular complications: nephropathy, retinopathy, damage to the blood vessels of the heart and brain, and peripheral vessels of the lower extremities. This is the main cause of disability and mortality in patients with diabetes. Therefore, type 2 diabetes is an acute medical and social problem.

ORAL GLOW-REDUCERS FACILITIES

In accordance with the application points, PSS are divided into three groups:

1) enhancing insulin secretion: stimulating the synthesis and/or release of insulin by β-cells or increasing the sensitivity of β-cells to physiological stimuli - sulfonylurea drugs, non-sulfonylurea secretagogues (glinides);

2) reducing insulin resistance (increasing sensitivity to insulin): suppressing increased glucose production by the liver and increasing glucose utilization by peripheral tissues; this includes biguanides and thiazolidinediones (glitazones);

3) suppressing the absorption of carbohydrates in the intestine: dietary plant fibers and resins; inhibitors (blockers) of a-glucosidases.

Since type 2 diabetes is a heterogeneous disease, the available arsenal of PSS allows us to influence various parts of its pathogenesis. β-cell dysfunction is characterized by a decrease in their number and decreased sensitivity to glucose. Impaired insulin secretion may be observed at the time of disease manifestation. There is a decrease in the first (early) phase of insulin secretion, and the concentration of proinsulin and its metabolic products increases. In addition, the phenomenon of glucotoxicity is revealed, which is expressed in an increase in the dysfunction of pancreatic β-cells under the influence of prolonged hyperglycemia. Therefore, the first choice drugs in these patients with type 2 diabetes (in cases where it is impossible to achieve adequate compensation for the disease through lifestyle modification—diet therapy in combination with physical activity) are PSMs.

Sulfonylurea derivatives. In 1942, M. Jeanbon and colleagues, while studying antibacterial sulfonamides, accidentally discovered their side effect in the form of hypoglycemia in laboratory animals. In the early 50s, clinical trials of tolbutamide, the first drug from this group, were carried out,

which was widely used. Sulfonylurea derivatives are usually divided into two generations. The first generation includes tolbutamide, acetohexamide, tolazamide and chlorpropramide. The second generation includes glibenclamide, glipizide, gliclazide, gliquidone and glimepiride. Second-generation drugs have a more pronounced hypoglycemic effect compared to first-generation drugs [8]. Therefore, they are prescribed in significantly smaller doses (measured in milligrams, and not in grams, like 1st generation drugs). Due to smaller doses, they have fewer side effects, interact less frequently with other drugs, and are available in more convenient forms. Currently, 1st generation PSMs, with the exception of chlorpropamide, are practically not used. The mechanism of the hypoglycemic effect is associated with stimulation of insulin secretion by β-cells under the

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influence of PSM on specific sulfonylurea receptors (SUR 1) and blocking of ATP-dependent potassium channels, which leads to activation of calcium channels, calcium entry into the cell and exocytosis of secretory granules. Drugs in this group also stimulate the secretion of somatostatin and slightly suppress the secretion of glucagon. An extrapancreatic effect of PSM was also noted (that is, an effect at the level of target tissues, an increase in the density of insulin receptors on monocytes, erythrocytes and lipocytes, the ability to suppress gluconeogenesis in the liver, etc.), which is probably due to a decrease in the manifestation of the phenomenon of glucose toxicity due to insulin secretion. The use of PSM in patients with type 2 diabetes initially increases the secretion of insulin by β-cells of the pancreas and reduces the hepatic clearance of insulin, which leads to an increase in this hormone in the blood. During the first months of treatment, fasting plasma insulin concentrations and insulin secretion in response to glucose intake increase. Subsequently, there is a drop in insulin concentration to the initial level (that is, what was before the start of treatment), but a sharp increase in glucose levels does not occur. This may be explained by the fact that a long-term decrease in glucose levels leads to restoration of tissue sensitivity to insulin. The decrease in the stimulating effect of PSMs with their long-term administration is due to a decrease in the number of sulfonylurea receptors on β-cells. If treatment is suspended, the β-cell response to the drug will be restored.

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