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POTENTIAL RISKS AND PHARMACOLOGICAL SAFETY FEATURES OF HYPOGLYCEMIC DRUGS

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Abstract

For the treatment of diabetes, insulin preparations, synthetic hypoglycemic agents, herbal medicine and compulsory adherence to the diet. Oral hypoglycemic agents belong to different chemical classes: sulfonylurea derivatives, biguanides, thiazolidinediones, etc. They can also be divided into secretogens (stimulate pancreatic insulin secretion, especially in the presence of glucose) and prandial (food-related) glycemic regulators (lower glucose in the blood after eating). As for the pharmacological safety of oral antidiabetic agents, they are incompatible with adrenal cortex hormones, adrenomimetics, MAO inhibitors, psychostimulants, antiarrhythmic agents. Their hypoglycemic effect is weakened by estrogens, gestagens, oral contraceptives, chlorpromazine, barbiturates, phenothiazines, thyroid hormones, glucagon, lithium salts, saluretics, indomethacin, drugs containing nicotinic acid.

Keywords: *hypoglycemic drugs, potential risks, pharmacological safety*

For the treatment of diabetes, insulin preparations, synthetic hypoglycemic agents, herbal medicine and compulsory adherence to the diet. Oral hypoglycemic agents belong to different chemical classes: sulfonylurea derivatives, biguanides, thiazolidinediones, etc. They can also be divided into secretogens (stimulate pancreatic insulin secretion, especially in the presence of glucose) and prandial (food-related) glycemic regulators (lower glucose in the blood after eating) [28, 15, 3, 13].

Mandatory requirements for hypoglycemic drugs:

- ✓ Convenience on application (1-2 times a day).
- ✓ Minimal risk of hypoglycemia.
- ✓ Absence of nephro-, hepato-, cardiotoxicity.
- ✓ Lack of interaction with other drugs.
- ✓ Favorable effect on the state of target organs, mainly suffering from diabetes [15, 13].

Sulfonylurea derivatives bind to specific receptors on the surface of pancreatic β-cell membranes, which leads to the closure of ATP-dependent potassium channels and depolarization of β-cell membranes. As a result, calcium channels open, calcium enters the cells and increases the secretion of insulin from the pancreas [32, 31]. Sulfonylurea derivatives act in the presence of functionally capable β-cells in the pancreas [13].

Sulfonylurea derivatives are divided into drugs of medium duration of action (8-24 hours) - tolbutamide, carbutamide and long-acting (24-60 hours) - glibenclamide, glyvidone, gliclazide [39].

The use of most sulfonylurea derivatives is accompanied by the development of severe hypoglycemia. The main difference between the second and third generation drugs from the first is their greater activity (50-100 times) and a lower risk of side effects [41].

Carbutamide, unlike tolbutamide, has a bactericidal effect on the intestinal flora [21, 37].

Glibenclamide in smaller doses exhibits a stronger hypoglycemic effect; reduces platelet aggregation, improves microcirculation in patients with diabetes, complicated by angiopathy, thrombophlebitis; has an antidiuretic effect. The action of glibenclamide lasts about 24 hours, which stimulates insulin secretion during the day and reduces the risk of hypoglycemia [10, 35].

Gliclazide improves microcirculation in organs and tissues; inhibits platelet adhesion and aggregation; with microangiopathies, it increases the reaction of blood vessels to adrenaline; improves the balance of PG, normalizes vascular permeability and prevents the development of atherosclerosis; does not lead to an increase in body weight. Hypoglycemic effect of gliclazide develops gradually, in terms of effectiveness it is inferior to glibenclamide [30, 4, 40].

Gliquidone is one of the well-tolerated hypoglycemic drugs that can be used in diabetic patients with liver and kidney diseases. [33].

Glipizide is available in two dosage forms: traditional and new - GIST (gastrointestinal therapeutic system), in which the drug is delivered from the tablet to the gastrointestinal tract carried out until the osmotic gradient changes [28, 13, 11].

Glimepiride is a third-generation drug, one of the most active sulfonylurea derivatives. The drug does not disrupt the activity of the cardiovascular system, does not accumulate, reduces the risk of retino-, neuro- and nephropathy, does not cause hypoglycemia, because contacts with the sulfonylurea receptor on the surface of the β-cell in a very short time. When used in combination, it can reduce the dose of insulin by 38% in obese patients [22].

Biguanides reduce the absorption of glucose in the intestine, inhibit gluconeogenesis in the liver and glycogenolysis, increase the peripheral utilization of glucose by tissues, reduce the glycogen content in the liver, inhibit insulin inactivation, i.e. mainly at the level of the liver eliminate insulin resistance, increase the sensitivity of receptors to insulin [15, 13, 8]. These drugs lower blood glucose levels only in the presence of endogenous or exogenous insulin [27].

Metformin enhances the process of fibrinolysis, inhibits platelet aggregation and the development of atherosclerosis [7]. Unlike insulin, it inhibits lipogenesis and stimulates lipolysis, reduces the level of glucagon in blood plasma, but creates an insignificant risk of lactic acidosis [19]. The advantage of metformin over drugs that stimulate insulin secretion is the absence of pronounced hypoglycemic reactions [20]. Biguanides can be combined with sulfonylureas drugs [34].

Thiazolidinediones derivatives modulate the transcription of insulin-sensitive genes, since they are agonists of nuclear PPAR-g receptors

(peroxisome proliferation-activated receptor) [24]. Thus, they take part in the control of glucose levels, lipid metabolism in adipose, muscle tissues and liver ; increase the sensitivity of receptors to insulin and eliminate insulin resistance at the level of peripheral tissues [1, 20].

Thiazolidinediones are used only in patients with clear signs of insulin resistance and preserved insulin secretion. Their advantage is the absence of hypoglycemia and the relative safety of use; disadvantage - low efficiency with monotherapy and the need for multiple doses [23].

Rosiglitazone improves the transmission of the insulin signal, reduces the level of free fatty acids in the blood, triglycerides, increases the content of cholesterol and HDL, enhances metabolic processes [12].

Pioglitazone is used only with preserved insulin-synthetic function of the pancreas [14, 6].

Acarbose blocks intestinal α-glucosidase enzymes involved in the breakdown of di-, oligo- and polysaccharides to monosaccharides, and inhibits their absorption in the small intestine [5]. Acarbose reduces the absorption of carbohydrates from food and the flow of glucose into the blood, smoothes fluctuations in blood glucose levels throughout the day; prevents the development of hyperglycemia that occurs after a meal [26]. It is an antihyperglycemic, not a hypoglycemic drug, but it can potentiate the hypoglycemic effect of other oral antidiabetic agents [9, 17].

Meglitinides stimulate insulin secretion by β-cells only in the presence of glucose by binding to a specific site of the ATP-dependent potassium channel [36, 25].

In terms of the strength of the hypoglycemic effect, meglitinides are comparable to sulfonylureas drugs[15]. The main direction of their action is to eliminate postprandial peaks of hyperglycemia, the frequency of taking drugs is equal to the frequency of food intake [13].

Repaglinide induces an insulinotropic response to food intake within 30 minutes after administration and lowers blood glucose levels during the meal [38, 29]. Nateglinide, a derivative of the amino acid D-phenylalanine, is an analogue of repaglinide [18, 16].

Glibomet is a combination of Metoformin and Glibenclamide; allows you to achieve the desired hypoglycemic effect with a lower dose of each component and reduce the risk of side effects in comparison with monotherapy [2].

As for the pharmacological safety of oral antidiabetic agents, they are incompatible with adrenal cortex hormones, adrenomimetics, MAO inhibitors, psychostimulants, antiarrhythmic agents [13]. Their hypoglycemic effect is weakened by estrogens, gestagens, oral contraceptives, chlorpromazine, barbiturates, phenothiazines, thyroid hormones, glucagon, lithium salts, saluretics, indomethacin, drugs containing nicotinic acid [28].

Antifungal agents (derivatives of azoles), fluoroquinolones, clofibrate, H2-histamine blockers, ACE inhibitors, NSAIDs, sulfonamides, anti-tuberculosis drugs, insulin, anabolic steroids, androgens, cyclophosphamide derivatives, alcohol enhance the hypoglycemic effect of oral hypoglycemic agents [15].

Sulfonylurea derivatives are incompatible with paracetamol, H2-histamine blockers, anti-tuberculosis drugs, cyclophosphamide derivatives [31]. These drugs cannot be combined with antibiotics, sulfonamides, because they are displaced from the connection with albumin, their free fraction in the blood increases and hypoglycemia occurs [32].

The simultaneous administration of anticoagulants of the dicumarin group, salicylates, tetracyclines, chloramphenicol, phenylbutazone with sulfonylurea derivatives leads to inhibition of the metabolic process of the latter, to their displacement from the connection with proteins and an increase in hypoglycemic activity [15]. Sulfonylurea hypoglycemia differs from insulin hypoglycemia in a prolonged course [32, 31]. They are carefully prescribed with β-blockers and anabolic agents. Tolbutamide is incompatible with phenylephrine, caffeine, isoprenaline sulfate. The action of biguanides is potentiated by salicylates and sulfonylureas agents [8].

With long-term use of metformin, the absorption of vitamin B12, folic acid, amino acids, bile acids, water may be impaired [27].

Glipizide should not be administered concomitantly with miconazole. With the simultaneous administration of glibomet with sulfonylurea derivatives, acarbose, insulin,

oxytetracycline, cyclophosphamide, its effect may be enhanced [13].

The action of acarbose is weakened by simultaneous administration with enzyme preparations, cholestyramine, antacids, intestinal adsorbents [26, 9].

As for the conditions for the rational use of hypoglycemic agents, alcohol intolerance arises during the treatment with sulfonylurea drugs. Blood and urine tests should be done monthly [31].

When administered to pregnant women, tolbutamide can interfere with the binding of bilirubin to protein and cause fetal hyperbilirubinemia. At the beginning of treatment with glibenclamide, it is possible to slow down the speed of psychomotor reactions, which affects the ability to drive vehicles and mechanisms control. With glibenclamide treatment, the incidence of hypoglycemia is especially high. It should be used with particular caution in persons who have had liver disease [35]. During physical exertion and stressful situations, the hypoglycemic effect of glycidone, glimepiride increases. In case of injuries, severe infections, extensive surgical interventions, a transfer of the patient from glipizide to insulin is required. During the use of glipizide, its rapid entry into the blood should be taken into account and in the first 4-5 days, the dose should be monitored according to the glycemic profile.

Biguanides should be used with caution in the elderly, and should not be prescribed with a low-calorie diet [19]. Pioglitazone in premenopausal women with anovulatory cycle can induce ovulation and increase the risk of pregnancy [6].

Glibomet is a combined drug, represented by two drugs of different classes. The synergistic effect allows you to reduce the dose of each component, which reduces the risk of side effects [13].

Lactic acidosis is reduced by intravenous administration of large amounts of sodium hidrocarbonate. Hypoglycemic drugs are dosed individually, taking into account the glucose content in the blood and urine [15]. The transition of patients who were treated with insulin to oral hypoglycemic agents is made if the daily dose of insulin was less than 40 units.

Glibenclamide, gliclazide, glipizide, acarbose, repaglinide, nateglinide are taken before meals; regardless of food intake - pioglitazone; with meals - glycvidone, metformin [15].

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Table 1. Comparative characteristics of oral hypoglycemic agents

Drugs	Hypoglycemic activity	T ½, h	Action (h)	
			Start	Duration
Tolbutamide	1	5-6	1	10-12
Carbutamide	++	36	5	12
Metformin	++	6-17	2	16
Glibenclamide	150-200	4-11	1,5-2	18
Glickvidone	+++	1,5	1-2	8-12
Glimepiride	200-250	5-8	2-3	24
Glipizides	++	2-5	30 min	> 24
Pioglitazone		3-7	2-3	24
Repaglinide		1	1,5-2	12
Roziglitazone		3-4	30-40 min	10-12