IJIMM, Volume 2, Issue 1, 2024
ISSN: 2995-5319
http://medicaljournals.eu/index.php/IJIMM

INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

CLINICAL PHARMACOLOGY OF HYPOGLYCEMIC DRUGS

Baymuradov Murodjon Chori o'g'li
Umirov Bekzod Safarovich
Department of Pharmacology and Clinical Pharmacology,
Termiz branch of the Tashkent Medical Academy
Research advisor: Senior teacher of the Department of Pharmacology and Clinical Pharmacology, Termiz branch of the Tashkent Medical Academy

Mahmaraimov Shavkat Tuxtashovich
mahmaraimovshavkat@gmail.com
Termiz Branch of Tashkent Medical Academy. Uzbekistan.

Abstract: Hypoglycemic drugs are used in the group of metabolic diseases with carbohydrate metabolism disorders, especially diabetes. Different drugs are used depending on the individual characteristics of this disease, the level of compensation and the presence of complications, which allows for individual therapy. Therefore, this article provides detailed information about the use of hypoglycemic drugs and their mechanism of action.

Keywords: metformin; meglitinide; gliptin; derivative sulfonylureas; thiazolidinedione; α-glucosidase inhibitor

The action of sulfonylurea derivatives is mainly associated with stimulation of pancreatic beta cells, accompanied by mobilization and increased release of endogenous insulin. The main prerequisite for the manifestation of their effect is the presence of functionally active beta cells in the pancreas. On the beta cell membrane, sulfonylurea derivatives bind to specific receptors associated with ATP-dependent potassium channels. The sulfonylurea receptor gene has been cloned. The classical high-affinity sulfonylurea receptor (SUR-1) was found to be a protein with a molecular mass of 177 kDa. Unlike other sulfonylureas, glimepiride binds to another ATP-dependent potassium channel-coupled protein with a molecular weight of 65 kDa (SUR-X). In addition, the K+ channel includes the intramembrane subunit Kir 6.2 (a protein with a molecular weight of 43 kDa), which is responsible for the transport of potassium ions. It is believed that as a result of this interaction, the potassium channels of the beta cells are "closed." An increase in the concentration of K+ ions inside the cell promotes membrane depolarization, the opening of voltage-dependent Ca2+ channels, and an increase in the intracellular content of calcium ions. The result of this is the release of insulin stores from the beta cells.

With long-term treatment with sulfonylurea derivatives, their initial stimulating effect on insulin secretion disappears. It is believed that this is due to a decrease in the number of receptors on beta cells. After a break in treatment, the response of beta cells to drugs of this group is restored.

Some sulfonylureas also have extrapancreatic effects. Extrapancreatic effects are of little clinical significance; they include an increase in the sensitivity of insulin-dependent tissues to endogenous insulin and a decrease in glucose production in the liver. The mechanism for the development of these effects is due to the fact that these drugs (especially glimepiride) increase the

INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

number of insulin-sensitive receptors on target cells, improve insulin-receptor interaction, and restore post-receptor signal transduction.

In addition, there is evidence that sulfonylurea derivatives stimulate the release of somatostatin and thereby suppress glucagon secretion.

Sulfonylurea derivatives:

I generation: tolbutamide, carbutamide, tolazamide, acetohexamide, chlorpropamide.

II generation: glibenclamide, glisoxepide, glibornuril, gliquidone, gliclazide, glipizide.

III generation: glimepiride.

The main difference between the second generation drugs and the first generation sulfonylurea derivatives is their greater activity (50–100 times), which allows them to be used in lower doses and, accordingly, reduces the likelihood of side effects. Individual representatives of hypoglycemic sulfonylurea derivatives of the 1st and 2nd generation differ in activity and tolerability. Thus, the daily dose of first generation drugs - tolbutamide and chlorpropamide - is 2 and 0.75 g, respectively; and second generation drugs - glibenclamide - 0.02 g; gliquidone - 0.06–0.12 g. Second generation drugs are usually better tolerated by patients.

Sulfonylurea drugs have different severity and duration of action, which determines the choice of drugs when prescribed. Glibenclamide has the most pronounced hypoglycemic effect of all sulfonylurea derivatives. It is used as a standard for assessing the hypoglycemic effect of newly synthesized drugs. The powerful hypoglycemic effect of glibenclamide is due to the fact that it has the greatest affinity for ATP-dependent potassium channels of pancreatic beta cells. Currently, glibenclamide is produced both in the form of a traditional dosage form and in the form of a micronized form - a form of glibenclamide crushed in a special way, providing an optimal pharmacokinetic and pharmacodynamic profile due to rapid and complete absorption (bioavailability - about 100%) and making it possible to use drugs in in smaller doses.

Gliclazide is the second most commonly prescribed oral hypoglycemic agent after glibenclamide. In addition to the fact that gliclazide has a hypoglycemic effect, it improves hematological parameters, rheological properties of blood, and has a positive effect on the hemostasis and microcirculation system; prevents the development of microvasculitis, incl. damage to the retina of the eye; suppresses platelet aggregation, significantly increases the relative disaggregation index, increases heparin and fibrinolytic activity, increases heparin tolerance, and also exhibits antioxidant properties.

Gliquidone is a drug that can be prescribed to patients with moderately severe renal impairment, because Only 5% of metabolites are excreted through the kidneys, the rest (95%) through the intestines.

Glipizide, having a pronounced effect, poses minimal danger in terms of hypoglycemic reactions, since it does not accumulate and has no active metabolites.

INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

Oral antidiabetic drugs are the mainstay of drug therapy for type 2 (non-insulin-dependent) diabetes mellitus and are usually prescribed to patients over 35 years of age without ketoacidosis, nutritional deficiency, complications or comorbidities requiring immediate insulin therapy.

Sulfonylurea drugs are not recommended for patients whose daily insulin requirement exceeds 40 units with a proper diet. They are also not prescribed to patients with severe forms of diabetes mellitus (with severe beta-cell deficiency), with a history of ketosis or diabetic coma, with hyperglycemia above 13.9 mmol/l (250 mg%) on an empty stomach and high glucosuria during diet therapy.

Transferring patients with diabetes mellitus on insulin therapy to treatment with sulfonylurea drugs is possible if disturbances in carbohydrate metabolism are compensated for with insulin doses of less than 40 units/day. At doses of insulin up to 10 units/day, you can immediately switch to treatment with sulfonylurea derivatives.

Long-term use of sulfonylurea derivatives can cause the development of resistance, which can be overcome by combination therapy with insulin drugs. In type 1 diabetes mellitus, the combination of insulin preparations with sulfonylurea derivatives makes it possible to reduce the daily need for insulin and helps to improve the course of the disease, including slowing the progression of retinopathy, which is to a certain extent associated with the angioprotective activity of sulfonylurea derivatives (especially the second generation). However, there are indications of their possible atherogenic effect.

In addition to the fact that sulfonylureas are combined with insulin (this combination is considered appropriate if the patient's condition does not improve with more than 100 units of insulin per day), they are sometimes combined with biguanides and acarbose.

When using sulfonamide hypoglycemic drugs, it should be taken into account that antibacterial sulfonamides, indirect anticoagulants, butadione, salicylates, ethionamide, tetracyclines, chloramphenicol, cyclophosphamide inhibit their metabolism and increase their effectiveness (hypoglycemia may develop). When sulfonylurea derivatives are combined with thiazide diuretics (hydrochlorothiazide, etc.) and CCBs (nifedipine, diltiazem, etc.) in large doses, antagonism occurs - thiazides interfere with the effect of sulfonylurea derivatives due to the opening of potassium channels, and CCBs disrupt the flow of calcium ions into the beta cells of the pancreas glands.

Sulfonylureas enhance the effects and intolerance of alcohol, probably due to a delay in the oxidation of acetaldehyde. Antabuse-like reactions are possible.

All sulfonamide hypoglycemic drugs are recommended to be taken 1 hour before meals, which contributes to a more pronounced decrease in postprandial (after meals) glycemia. In case of severe dyspeptic symptoms, it is recommended to use these drugs after meals.

Undesirable effects of sulfonylurea derivatives, in addition to hypoglycemia, are dyspeptic disorders (including nausea, vomiting, diarrhea), cholestatic jaundice, weight gain, reversible leukopenia, thrombocytopenia, agranulocytosis, aplastic and hemolytic anemia, allergic reactions (including itching, erythema, dermatitis).

INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

The use of sulfonylureas during pregnancy is not recommended, because Most of them belong to class C according to the FDA (Food and Drug Administration, USA), and insulin therapy is prescribed instead.

Elderly patients are not recommended to use long-acting drugs (glibenclamide) due to the increased risk of hypoglycemia. At this age, it is preferable to use short-acting derivatives - gliclazide, gliquidone.

Meglitinides are prandial regulators (repaglinide, nateglinide).

Repaglinide is a derivative of benzoic acid. Despite the difference in chemical structure from sulfonylurea derivatives, it also blocks ATP-dependent potassium channels in the membranes of functionally active beta cells of the pancreatic islet apparatus, causes their depolarization and the opening of calcium channels, thereby inducing insulin incretion. The insulinotropic response to food intake develops within 30 minutes after administration and is accompanied by a decrease in blood glucose levels during the meal period (insulin concentrations do not increase between meals). As with sulfonylureas, the main side effect is hypoglycemia. Repaglinide should be prescribed with caution to patients with hepatic and/or renal insufficiency.

Nateglinide is a derivative of D-phenylalanine. Unlike other oral hypoglycemic agents, the effect of nateglinide on insulin secretion is more rapid but less persistent. Nateglinide is used primarily to reduce postprandial hyperglycemia in type 2 diabetes.

Biguanides, which began to be used to treat type 2 diabetes in the 1970s, do not stimulate insulin secretion by pancreatic beta cells. Their action is mainly determined by inhibition of gluconeogenesis in the liver (including glycogenolysis) and increased utilization of glucose by peripheral tissues. They also inhibit the inactivation of insulin and improve its binding to insulin receptors (this increases the absorption of glucose and its metabolism).

Biguanides (unlike sulfonylurea derivatives) do not reduce blood glucose levels in healthy people and in patients with type 2 diabetes after an overnight fast, but significantly limit its increase after a meal without causing hypoglycemia.

Hypoglycemic biguanides - metformin and others - are also used for type 2 diabetes mellitus. In addition to their hypoglycemic effect, biguanides have a positive effect on lipid metabolism with long-term use. Drugs in this group inhibit lipogenesis (the process by which glucose and other substances are converted into fatty acids in the body), activate lipolysis (the process of breaking down lipids, especially triglycerides contained in fat, into their constituent fatty acids under the action of the lipase enzyme), reduce appetite, and promote reduction in body weight. In some cases, their use is accompanied by a decrease in the content of triglycerides, cholesterol and LDL (determined on an empty stomach) in the blood serum. In type 2 diabetes mellitus, carbohydrate metabolism disorders are combined with pronounced changes in lipid metabolism. Thus, 85–90% of patients with type 2 diabetes mellitus have increased body weight. Therefore, when type 2 diabetes mellitus is combined with excess body weight, drugs that normalize lipid metabolism are indicated.

INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

The indication for the prescription of biguanides is type 2 diabetes mellitus (especially in cases accompanied by obesity) with the ineffectiveness of diet therapy, as well as with the ineffectiveness of sulfonylurea drugs.

References:

1. Butterworth J. Local anesthetics: pharmacology and clinical use. // Anesth. Analg.- 2002.-V.94 (3 Suppl S).- P.22-26.
2. Carpenter R. Local anesthetic toxicity: the case for ropivacaine. // Am.J.Anesthesiol.- 1997.- V.24 (5, Suppl).- P.4-7.
3. McClure J. Ropivacaine. // Br. J. Anaesth. –1996. –V.76. – P.300-307.
4. Rosenberg P. Maximum recommended doses of local anaesthetics – need for new recommendations? // Highlights in Regional Anaesthesia and Pain Therapy. XI. – Special Edition World Congress on Regional Anaesthesia and Pain Therapy – Barselona, Spain, 2002. – P.30-34.