Features of Prescribing Modern Sugar-Lowering Drugs to Patients with Type 2 Diabetes Mellitus

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ABSTRACT

The number of patients with type 2 diabetes mellitus (DM2) is steadily increasing. According to Diabetes Atlas 2021, there are 536 million people with type 2 diabetes worldwide. At the same time, experts say that the number of undiagnosed diabetes mellitus (DM) may exceed the level recorded today by 2-3 times. Therefore, rational pharmacotherapy of this disease is the subject of numerous scientific and clinical studies. One of the largest recent studies has been the UK Diabetes Control and Complications Prospective Study (UKPDS). It lasted for about 20 years more than 5000 patients with type 2 diabetes participated in it. Patients were divided into groups who received different types of treatment since the moment of DM detection: only diet, various oral hypoglycemic drugs, insulin therapy.

KEYWORDS: *diabetes mellitus, hyperglycemia, insulin resistance, secretagogues..*

The study showed the possibility of reducing the frequency of complications of the disease with intensive treatment tactics. It has been demonstrated that a 1% decrease in the level of glycated hemoglobin HbA1c (as a result of intensive treatment of diabetes using various methods for 10 years) reduces the incidence of complications of diabetes in general by 21%, microvascular complications by 35%, myocardial infarction by 18%, stroke by 15%, diabetes mortality by 25%, total mortality by 17%. Taking into account the great danger of chronic (and often not realized by patients and even doctors) decompensation of DM in terms of the development of vascular complications, in recent years more stringent criteria for compensation (more precisely, treatment goals) for DM2 have been developed (Table 1) and some therapeutic approaches to this group of patients. The selection of adequate hypoglycemic therapy and the achievement of the desired degree of compensation for the disease in patients with type 2 diabetes present certain difficulties. This is due to the significant heterogeneity of DM2, which makes it difficult to search for pathogenetic treatment in each specific case [5,7].

The appointment of oral hypoglycemic drugs (OSBP) for newly diagnosed type 2 diabetes is recommended if proper diet in combination with physical activity does not lead to compensation of carbohydrate metabolism.[1] Unfortunately, it is often necessary to prescribe PSSP with persistent decompensation of DM against the background of a clear non-compliance with the diet. An alternative here could be a referral to the "School of Diabetes" for group training in order to change attitudes to nutrition, or to involve a psychologist in the process of changing the patient's behavior. To date, the following classes of PSSPs are used in clinical practice:

1. Sulfonylureas
2. Biguanides
3. Dipeptyl peptidase 4 inhibitors

4. glucagon-like peptide 1 agonists

5. Thiazolidinediones

6. Combined drugs.

The mechanisms of action of these classes of drugs are different, but in general they are aimed at eliminating the three main metabolic disorders that lead to hyperglycemia: impaired insulin secretion by the pancreas, peripheral insulin resistance, and excessive production of glucose by the liver. An additional mechanism of action is to slow down the absorption of glucose in the small intestine and thereby reduce the postprandial rise in glycemia [3].

Derivatives of sulfonylurea. Despite the fact that patients with type 2 diabetes have hyperinsulinemia (at least at the beginning of the disease), to overcome the existing insulin resistance, their own insulin is not enough and it is necessary to increase the concentration of the hormone in the blood with medication. Sulfonylureas (PSM) belong to the group of secretogogues, i.e. their action is based primarily on the ability to stimulate the secretion of insulin by pancreatic b-cells, especially in the presence of glucose. The drugs of this group bind to specific receptors on the surface of b-cell membranes. This binding leads to the closure of ATP-dependent potassium channels and depolarization of the membranes of b-cells, which, in turn, promotes the opening of calcium channels and the rapid entry of calcium into these cells. This process leads to degranulation and secretion of insulin. Thus, SCMs activate the same natural mechanism by which glucose stimulates insulin secretion. An increase in the level of insulin in the blood ensures the utilization of glucose by insulin-dependent tissues and the suppression of glucose production by the liver. PSM are divided into drugs of the first and second and third generation [4]. The main difference between the drugs of the second and third generation from the first is their greater activity. Thus, third-generation drugs have a 50-100 times more pronounced hypoglycemic effect compared to those of the first generation, and therefore are used in much lower doses. Accordingly, the risk of side effects in the latest generation of drugs is lower than in the first. Currently, only third-generation PSMs are used in clinical practice. All PSM have a generally similar structure, and their pharmacological effect is mediated through a single mechanism. But, some differences in the chemical structure lead to the fact that each of them has its own characteristics of action, which allow them to be optimally used in certain situations[3].

Assign PSM with minimal doses, gradually (with an interval of 1-2 weeks) evaluating the effect and increasing the dose as needed. In each case, the dose of the drug should be selected individually, keeping in mind the high risk of hypoglycemic conditions in the elderly.

Glibenclamide remains one of the most widely used PSMs in the world. It has the highest affinity for ATP-dependent K-channels of b-cells, and therefore has a powerful hypoglycemic effect, often causing hypoglycemia, usually in the event of a violation of the diet or indications for its use. Currently, both non-micronized and micronized forms of glibenclamide are used. The bioavailability of the non-micronized form is up to 70%, and the concentration in the blood reaches a maximum 4-6 hours after taking the drug orally. The half-life is from 10 to 12 hours, the hypoglycemic effect lasts up to 24 hours. It is excreted from the body by 50% by the kidneys and by 50% with bile. The daily dose can vary from 2.5 to 20 mg (usually 10-15 mg) and is usually prescribed in 1-2 doses. Often used in common practice, the appointment of 3 doses is not justified in terms of increasing its effectiveness. Usually the ratio of the morning and evening dose is 1:1 or 2:1. The drug is taken 30 minutes before meals. The micronized forms that have appeared in recent years (1.75 and 3.5) are characterized by almost complete bioavailability, special pharmacokinetics, pharmacodynamics and greater efficiency when used in a smaller single and daily dose. The micronized form of glibenclamide provides complete release of the active substance within 5 minutes after dissolution

and rapid absorption, and therefore the interval between taking the drug and food can be reduced. The maximum concentration of micronized glibenclamide also occurs earlier, i. better coincides with the peak of postprandial glycemia. The duration of the hypoglycemic effect of micronized forms is up to 24 hours, and due to the complete bioavailability of the drug, the need for glibenclamide is lower by 30–40%, which ultimately ensures adequate secretion of insulin during the day and reduces the risk of hypoglycemic conditions. The maximum dose of micronized glibenclamide is 14 mg/day[6,9].

Gliclazide (Diabeton*),* in addition to the hypoglycemic effect (softer than that of glibenclamide), it has a positive effect on microcirculation, the hemostasis system, some hematological parameters and blood rheological properties, which is extremely important for patients with diabetes. It is also believed that gliclazide most well stimulates the early phase of insulin secretion, which is impaired in T2DM. The half-life is 12 hours, so it is most often used in 2 divided doses. It is metabolized in the liver, most of it is excreted by the kidneys. The initial daily dose is 40-80 mg, the maximum is 320 mg. More recently, a new modified-release form of gliclazide, Diabeton MB, has appeared [4,5]. Almost 100% bioavailability allowed to reduce the dose of gliclazide when using this form to 30-120 mg per day. The duration of action is 24 hours, so the drug is taken once a day before breakfast, so that the action profile corresponds to the normal daily rhythm of insulin release. This regimen, as well as the effect of gliclazide predominantly on the first phase of insulin secretion, provides a lower risk of hyperinsulinemia**.** The result of this milder action is a low incidence of hypoglycemia, no weight gain, and a relatively delayed development of secondary drug resistance.

Gliquidone is the only hypoglycemic drug, the appointment of which is possible in patients with kidney disease: 95% of the received dose of the drug is excreted through the gastrointestinal tract and only 5% through the kidneys. Due to the fact that, other hypoglycemic drugs are excreted largely through the kidneys, with diabetic nephropathy or concomitant kidney damage, there is a high risk of their cumulation with the development of severe hypoglycemia. The initial dose of 30 mg, in the absence of effect, it is gradually increased (if necessary, up to 120-180 mg). It should also be noted that, compared with other drugs, gliquidone is shorter-acting, so the frequency of administration can be increased up to 3 times a day.

Glimepiride has a number of specific features. It differs from other PSMs in that it binds not to the classical sulfonylurea receptor (with a molecular weight of 177 kD), but to another protein coupled to the ATP-dependent K-channels of b-cells and having a molecular weight of 65 kD. In this regard, the drug is 2.5-3 times faster than glibenclamide, causes the release of insulin by b-cells. On the other hand, the dissociation of its complex with the binding protein occurs 8–9 times faster than that of other PSMs. The long duration of the effect (24 hours) makes it sufficient to take 1 time per day, which reduces the likelihood of missing medication. At the same time, increased insulin secretion occurs almost exclusively during meals, which significantly reduces the risk of hypoglycemic conditions. A wide range of doses of glimepiride tablet forms (1, 2, 3, 4, 6 mg) facilitates the selection of the required daily dose and its intake by patients. The maximum dose is 8 mg [5].

In the treatment of patients with PSM, in some cases resistance to drugs of this group is observed. In the case when the absence of the expected hypoglycemic effect is observed from the first days of treatment, despite the change of drugs and an increase in the daily dose to the maximum possible, it is customary to speak of primary resistance to PSM, which is observed in 5% of newly diagnosed patients. As a rule, primary resistance to PSM is due to a decrease in the residual secretion of one's own insulin and dictates the need to transfer patients to insulin therapy. Secondary resistance to SSM usually develops several years after the start of treatment. Every year, this phenomenon is found in 5-10% of patients with type 2 diabetes. Some of these patients have more slowly progressive type 1 diabetes. In the treatment of such patients, insulin therapy is mandatory. In another group of patients,

a decrease in residual secretion of insulin is observed only with stimulation with glucose, and not with arginine, which indicates a decrease in the sensitivity of β-cell glucoreceptors to glucose. In some of these patients, the appointment of insulin therapy for a short time restores the sensitivity of glucoreceptors and allows you to return to oral hypoglycemic therapy. Secondary resistance to PSM can be caused by exacerbation of concomitant diseases. After stopping these conditions, the effectiveness of PSM can be restored. In some cases, there is not a true secondary resistance to PSM, but a deterioration in their effect due to non-compliance with the diet[6,8].

It is always necessary to be aware of the risk of hypoglycemic reactions when using PSM and warn patients about the need to carry easily digestible carbohydrates with them. Hypoglycemia is, rather, not a side effect, but a direct effect of PSM, but indicates an incorrect dose selection or a violation of the diet. A feature of hypoglycemia caused by PSM (unlike most "insulin" hypoglycemia) is their prolongation due to the long half-life of these drugs, especially in old age. Therefore, after successful removal from the state of hypoglycemia, it can still recur within 12-72 hours.

Side effects with the use of PSM are most often not severe. As a rule, they appear in the first 2 months from the start of therapy and are manifested by dyspeptic disorders in the form of nausea, sometimes vomiting, epigastric pain, and a metallic taste in the mouth. Much less common are more severe side effects that require a dose reduction or complete discontinuation of drugs. These are skin allergic reactions, leuko- and thrombocytopenia, agranulocytosis, hemolytic anemia, toxic damage to the liver and kidneys. Side effects of SSM include weight gain, but this effect can be minimized or prevented by proper dieting.

*Biguanides***.** The drugs of this group do not change the secretion of insulin, however, in the presence of the latter, they increase the peripheral utilization of glucose by tissues. The second important mechanism of action of biguanides is a decrease in gluconeogenesis and a decrease in glucose production by the liver. It is also believed that they can reduce the absorption of carbohydrates in the intestines. The effect of biguanides on blood sugar levels can be assessed as antihyperglycemic rather than hypoglycemic.

The most dangerous side effect of biguanides is the development of lactic acidosis, in connection with this, for a long time the attitude towards this group was very negative, but in the 90s one of the representatives of the biguanide group, metformin, was rehabilitated. It has been shown to have a minimal risk of developing lactic acidosis [4].

Metformin is relatively rapidly absorbed, from the gastrointestinal tract. At a daily dose of 0.5–1.5 g, bioavailability is 50–60%. Maximum saturation with the drug is usually achieved at a dose of 3 g. In this regard, the appointment of higher doses of metformin is considered inappropriate, since it does not further enhance the antihyperglycemic effect. Complete elimination of the drug usually occurs within 8-20 hours. The initial daily dose of metformin should not exceed 500 mg. The drug is taken with food. If necessary, after a week from the start of therapy (provided there are no side effects), the dose of the drug can be increased to 500 mg twice a day and beyond. The optimal daily dose of metformin is 1500-1700 mg (500 mg three times or 850 mg twice a day). The maximum effect of metformin treatment occurs after a few weeks - it should not be expected too early. With monotherapy, the decrease in HbA1c is 0.9–1.5%. In addition to the above effect of metformin on carbohydrate metabolism, its positive effect on lipid metabolism should be emphasized, which is no less important in DM2: a decrease in total cholesterol by 10%, triglycerides by 20–30%. Metformin is practically the only hypoglycemic drug, the treatment of which can lead not to an increase, but even to a decrease in the body weight of patients (on average, by 1.5 kg per year). If weight gain does occur over time, it is minimal compared to other drugs, according to the UKPDS study. Therefore, the indication for the use of metformin is the impossibility of achieving compensation for

the disease in people with DM2 (primarily with obesity) on the background of diet therapy alone or in combination with the use of SSM. Among the side effects of metformin, diarrhea and other dyspeptic symptoms (metallic taste in the mouth, nausea, anorexia) should be noted, which are observed in almost 20% of patients at the beginning of therapy, and then disappear on their own after a few days. The risk of side effects can be minimized by slowly titrating the dose, taking the drug with meals, and reducing doses when they occur. With long-term use of metformin in high doses, one should be aware of the possibility of reducing the absorption of vitamins B12 and folic acid in the gastrointestinal tract, which in exceptional cases can lead to the development of megaloblastic anemia. The risk of developing lactic acidosis with metformin is minimal compared to other biguanides and does not exceed 8.4 cases per 100,000 patients per year. Moreover, with the development of lactic acidosis, as a rule, it is not about metformin-induced, but metformin-associated acidosis. Lactic acidosis of varying severity can develop without taking medication - against the background of heart, kidney and liver failure, as well as when drinking alcohol. However, even such an insignificant risk of developing lactic acidosis should be borne in mind and the lactate content should be monitored (optimally - about twice a year), glomerular filtration rate should be regularly assessed (the development of renal failure of any origin will lead to metformin accumulation). If there are complaints of muscle pain, the level of lactate should be immediately investigated, and with an increase in the content of lactate or creatinine in the blood, treatment with metformin should be discontinued. The positive aspects of the action of metformin include the fact that by itself it is practically not capable of causing hypoglycemia [5, 6].

Contraindications to the appointment of metformin are hypoxic conditions of any nature, impaired liver and kidney function, heart failure, a tendency to abuse alcohol and an indication of the presence of lactic acidosis in history. Metformin should be stopped 1-2 days before any contrast study due to the risk of developing renal failure after intravenous contrast administration. Metformin can be used both as monotherapy with diet in people with type 2 diabetes and obesity, and in combination with SCM or insulin. The specified combination therapy is prescribed if the desired therapeutic effect against the background of monotherapy is not achieved.

Incretinomimetics. Incritins are a fairly new line of hypoglycemic drugs in the treatment of type 2 diabetes (glucagon-like polypeptide-1 receptor agonists). The regulation of blood glucose, in addition to insulin and glucagon, depends on the hormones incretins produced in the intestine in response to food intake. Up to 70% of postprandial insulin secretion in healthy individuals is due precisely to the effect of incretins.

The main representatives of incretins are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). The entry of food into the digestive tract rapidly stimulates the release of GIP and GLP-1. Incretins may also lower glycemic levels through non-insulin mechanisms by slowing gastric emptying and reducing food intake. In type 2 diabetes, the content of incretins and their effect are reduced, and the level of glucose in the blood is increased. The ability of GLP-1 to improve glycemic control is of interest in the treatment of type 2 diabetes [1, 2].

GLP-1 has multiple effects on the endocrine part of the pancreas, but its principal action is the potentiation of glucose-dependent insulin secretion. Increased levels of intracellular cyclic adenosine monophosphate (cAMP) stimulate GLP-1 receptors (rGLP-1), resulting in exocytosis of insulin granules from β-cells. An increase in cAMP is thus the primary mediator of GLP-1 induced insulin secretion. GLP-1 enhances insulin gene transcription, insulin biosynthesis, and promotes β-cell proliferation through rGLP-1 activation. GLP-1 also potentiates glucose-dependent insulin secretion via intracellular pathways.

Improvement in glycemia after administration of GLP-1 may result from the restoration of normal β-cell function. GLP-1 has an additional hypoglycemic effect that is not associated with an effect on the pancreas and stomach. In the liver, GLP-1 inhibits glucose production and promotes glucose uptake by adipose and muscle tissue, but these effects are secondary to regulation of insulin and glucagon secretion. [2, 3].

An increase in the mass of β-cells and a decrease in their apoptosis is a valuable quality of GLP-1 and is of particular interest for the treatment of type 2 diabetes, because the main pathophysiological mechanism is precisely the progressive beta-cell dysfunction.

Incretin mimetics used in the treatment of type 2 diabetes include 2 classes of drugs: GLP-1 agonists (exenatide, liraglutide) and inhibitors of DPP-4 dipeptidyl peptidase, which destroys GLP-1 (sitagliptin, vildagliptin).

Exenatide (Byeta) was isolated from the saliva of the giant lizard Gila monster. When exenatide is administered subcutaneously, its peak plasma concentration is reached after 2-3 hours, and the half-life is 2-6 hours. This allows therapy to be administered as two subcutaneous injections per day before breakfast and dinner. Created Exenatide LAR, administered once a week. The developed GLP-1 preparations do not have oral forms and require obligatory subcutaneous administration. This drawback is deprived of drugs from the group of DPP-4 inhibitors. The drugs of this group, due to the suppression of DPP-4 activity, increase the concentration of incretins (primarily GLP-1), which are secreted in the intestine during the day in response to food intake. At normal and elevated blood glucose levels, incretins increase the synthesis and secretion of insulin and reduce the secretion of glucagon, which normalizes glycemia. When blood sugar is low, the action of incretins on the production of insulin and glucagon is absent. The drugs are available in tablet form and are prescribed 1-2 times a day, which increases patient compliance [2, 3]. DPP-4 inhibitors include vildagliptin (Galvus, Novartis), recommended by the FDA (USA) and the EU for the treatment of type 2 diabetes, both as monotherapy and in combination with metformin, thiazolidinediones, and sulfonylurea derivatives. DPP-4 inhibitors are not prescribed for impaired liver function, pregnancy, lactation, and patients under 18 years of age. The usual dose of Galvus is 50 mg 1-2 times a day [2, 3].

Thiazolidinediones. Thiazolidinedione drugs (pioglitazone, rosiglitazone) have entered clinical practice only in recent years. Like biguanides, these drugs do not stimulate insulin secretion, but increase the sensitivity of peripheral tissues to it. Compounds of this class act as agonists of nuclear PPAR-g receptors (peroxisome proliferator-activated receptor). PPAR-g receptors are found in adipose, muscle and liver tissues. Activation of PPAR-g receptors modulates the transcription of a number of genes associated with the transmission of insulin effects on cells and involved in glucose control and lipid metabolism. In addition to lowering the level of glycemia, improving the sensitivity of tissues to insulin has a positive effect on the lipid profile (the level of high-density lipoproteins increases, the content of triglycerides decreases). Given that these drugs act by stimulating gene transcription, it takes up to 2-3 months to get the maximum effect. In clinical studies, these drugs provided a decrease in HbA1c levels when monotherapy was approximately 0.5-2%. This class of drugs can be used in combination with PSM, insulin or metformin. The combination with metformin is justified due to the fact that the action of biguanides is aimed more at suppressing gluconeogenesis, and the action of thiazolidinediones is aimed at increasing peripheral glucose utilization. They practically do not cause hypoglycemia (but, like biguanides, they can increase the frequency of hypoglycemia in combination with secretogogues).

The thiazolidinedione drug pioglitazone is currently registered. The drug, which belongs to the second generation of thiazolidinediones, was not found to have a hepatotoxic effect (the use of the

"first generation" drug troglitazone was prohibited because of this). Against the background of treatment, it is recommended to control the level of alanine- and aspartate transferase and stop taking the drug when the level of enzymes is twice the norm. Pioglitazone is inactivated in the liver, excreted mainly in the bile. One of the side effects may be the appearance of edema, as well as weight gain. The drug is prescribed once a day, regardless of meals. The daily dose varies from 15 to 45 mg.

*Combined drugs***.** Traditionally, DM2 treatment begins with monotherapy with metformin or PSM, and only with a pronounced deterioration in glycemic control, a second drug or insulin is added. This tactic leads to the fact that a fairly large proportion of DM2 patients are constantly in a state of unsatisfactory compensation, having glycated hemoglobin HbA1c at a level of at least 9%. The UKPDS study also noted the limited possibility of monotherapy with long-term maintenance of good glycemic control. At 3 years after diagnosis, only 50% were able to achieve the recommended HbA1c levels with monotherapy, and by year 9 this figure was less than 25%. It seems logical to have an intensive therapeutic effect at the earliest possible time simultaneously on both pathogenetic links that cause hyperglycemia in order to achieve a constant HbA1c level of less than 7%, recommended as a goal for the prevention of complications.

The use of two drugs of different classes in medium doses is more justified not only pathogenetically: such therapy creates a lower risk of severe side effects than high doses of one drug. But, on the other hand, combination therapy can lead to a decrease in patient compliance with treatment. In this regard, the question arose about the production of ready-made combinations. Currently, ready-made combinations of PSM and metformin are used.

Insulin therapy. The number of DM2 patients requiring insulin treatment is steadily increasing, having long exceeded the number of DM1 patients. Unfortunately, there are many reasons (more psychological than objective) due to which insulin therapy in T2DM is often prescribed too late and is considered as the "last resort" in the treatment of DM. In fact, given the heterogeneity of type 2 diabetes, it can be said that in some cases insulin should be administered very early, if not at all from the very beginning of the disease.

Conclusion. Modern treatment of T2DM requires a paradigm shift in the form of an appropriate intensification of therapy from the very diagnosis. Determination of the multicomponent pathogenesis of T2DM leads to an understanding of the need to influence the disease from different angles, i.e. simultaneous action on several mechanisms of development of hyperglycemia. The most important aspect in reducing the risk of complications of diabetes is the rapid achievement of carbohydrate metabolism compensation and its maintenance.

Therefore, the development of modern pharmacology and the development of new drugs in the treatment of type 2 diabetes is so important and remains relevant.

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