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TREATMENT OF TYPE 2 DM WITH NEW CLASS DRUGS: I DPP-4, A GLP-1, AND SGLT-2

[1]Kasimova Tahmina, [2]Ismailov S.I., [3]Nasirova H.K., [4]Narimova G.Zh.
[1,2,3]Tashkent Pediatric Medical Institute
[4]RSSPMC of Endocrinology named after Y.H. Turakulov
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Abstract. *The annual increase in patients with type 2 diabetes averages 12.3%. The largest number of patients with type 2 diabetes is patiants aged 51 to 58 years - 10.2% of men and 16.2% of women. Treatment of type 2 diabetes is aimed at minimizing the risk of developing micro- and macrovascular complications. The emergence of new antidiabetic drugs, the action of which is based on the enhancement of the effect of endogenous incretins, opens up new prospects in the treatment of type 2 diabetes. Despite the fact that 2 classes of these drugs (DPP-4 inhibitors and GLP analogs) belong to chemically different and structurally independent compounds, they have a similar mechanism of action, which consists in regulating glucose homeostasis by affecting the processes of glucose-dependent synthesis of insulin and glucagon, influencing consumption food and the promotion of chyme, on the proliferation, differentiation of pancreatic B-cells. A significant advantage of DPP-4 inhibitors is the possibility of their use in tablet form, unlike injectable GLP analogues. It is also important that DPP-4 inhibitors do not cause significant side effects, do not increase the incidence of hypoglycemia, and do not lead to weight gain. It has been shown that long-term subcutaneous administration of GLP-1 to patients with type 2 diabetes (for 6 weeks) improved the function of b-cells, reduced the level of glucose and glycosylated hemoglobin (HbA1c), and increased peripheral insulin sensitivity; in addition, a decrease in body weight of patients has been recorded. However, as already noted, the period of circulation of endogenous or exogenous GLP-1 in the blood is extremely short due to the rapid inactivation of incretins under the action of the dipeptidyl peptidase-4 enzyme. To ensure the practical use of native GLP-1 as a new agent in the treatment of type 2 DM, it is advisable to prevent the rapid breakdown of GLP-1 using DPP-4 inhibitors. Sodium-glucose cotransporter type 2 (SGLT2) inhibitors are a new class of oral antidiabetic drugs that reduce glycemia independently of insulin and beta-cell function.*

SGLT2 inhibitors, due to the unique mechanism of action that does not depend on the severity of insulin resistance and beta-cell deficiency, are equally effective both in patients with type 2 diabetes with a disease duration of less than one year and in patients with type 2 diabetes of a long course (more than ten years). All inhibitors are highly selective for SGLT2 over SGLT1. The safety of these drugs is due to an extremely narrow spectrum of action - inhibition of a specific protein, which is present almost exclusively in the epithelial cells of the proximal tubules of the nephron.

Keywords: *type 2 diabetes, incretins, mechanisms of action, new combinations of hypoglycemic drugs, glucagon-like peptide, SGLT.*

Treatment of type 2 diabetes is aimed at minimizing the risk of developing micro- and macrovascular complications.

Among the main directions in the treatment of type 2 diabetes, expected by experts from the USA, Europe, Japan, fundamentally recognized approaches have now been identified.

The emergence of new antidiabetic drugs, the action of which is based on the enhancement of the effect of endogenous incretins, opens up new prospects in the treatment of type 2 diabetes.

Despite the fact that 2 classes of these drugs (DPP-4 inhibitors and GLP analogs) belong to chemically different and structurally independent compounds, they have a similar mechanism of action, which consists in regulating glucose homeostasis by affecting the processes of glucose-dependent insuline and glucagon synthesis, influencing consumption food and the promotion of chyme, on the proliferation, differentiation of pancreatic B-cells.

One of the factors in the pathogenesis of type 2 diabetes is a violation of incretin-stimulated secretion of insulin by pancreatic beta cells.

Incretins are hormones produced in the small intestine that stimulate more than 50% of insulin secretion in response to oral carbohydrate intake.

Glucogon is produced by the alpha cells of the pancreas. Glucogon is formed from a large preglucogon peptide, which is encoded by the preglucogon gene located in humans on chromosome e 2.

In pancreatic alpha and L-cells of the small intestine, preglucagon is cleaved by prohormone convertase -1/3 into a number of peptides GLP1, GLP2.

GLP2 - small intestine cell growth regulator, involved in nutrient metabolism.

GLP1 is secreted by L cells in response to food intake and binds to its receptors, which are similar to those of glucagon.

In type 2 diabetes, the content of incretins and their effectiveness are reduced, and the glucose level is elevated.

Incretins include GLP1, a glucose-dependent insulinotropic polypeptide.

It was found that in type 2 DM, the secretion of GIP in response to food intake increases, and the secretion of GLP1- decreases.

ГПП1 повышает секрецию инсулина и подавляя высвобождение глюкогона из альфа клеток ПЖЖ и следовательно, глюконеогенеза в печени

GLP1 increases insulin secretion and inhibits the release of glucogon from pancreatic alpha cells and hence hepatic gluconeogenesis.

GLP1 slows gastric emptying and acts on the satiety center to reduce food intake, leading to weight loss.

GLP1 also has a beneficial effect on the cardiovascular system. They reduce blood pressure, reduce hypoxia, improve mircard function.

GLP-1 antigens are safe and well tolerated. They have a pronounced hypoglycemic effect (reduce the level of HbA1c), and, unlike insulin and other hypoglycemic agents, do not cause hypogoicemia.

Among a GLP1, Victoza is the most well-known.

Victoza significantly reduces

-level of glycated hemoglobin

- normalizes blood glucose levels

- prevents the development of hypoglycemia

- reduces blood pressure

-has a cardioprotective effect.

Some studies have shown an increase in the proliferation of pancreatic beta cells and a decrease in their apoptosis under the action of GLP1.

In the body, GLP1 is rapidly destroyed by the enzyme DPP4, and because of this, its effect is very short-lived.

Two classes of drugs have been developed: aGLP1 and iDPP4, which increase the concentration of endogenous GLP1 and slow down its degradation.

In the liver, GLP1 inhibits glucose production and promotes glucose uptake by adipose and muscle tissue.

An increase in the mass of beta cells and a decrease in their apoptosis is a valuable quality of GLP1 and is of particular interest for the treatment of type 2 diabetes, T. The main mechanism for the development of type 2 diabetes is precisely the progressive destruction of pancreatic beta cells

Incretin mimetics used in the treatment of type 2 diabetes include 2 classes of drugs:

1) AGPP1 (Byetta, Victoza)

2) iDPP4 (Sitagliptin, Vildagliptin (Galvus)

A significant advantage of DPP-4 inhibitors is the possibility of their use in tablet form, unlike injectable GLP analogues. It is also important that DPP-4 inhibitors do not cause significant side effects, do not increase the incidence of hypoglycemia, and do not lead to weight gain. It is appointed 1-2 times a day.

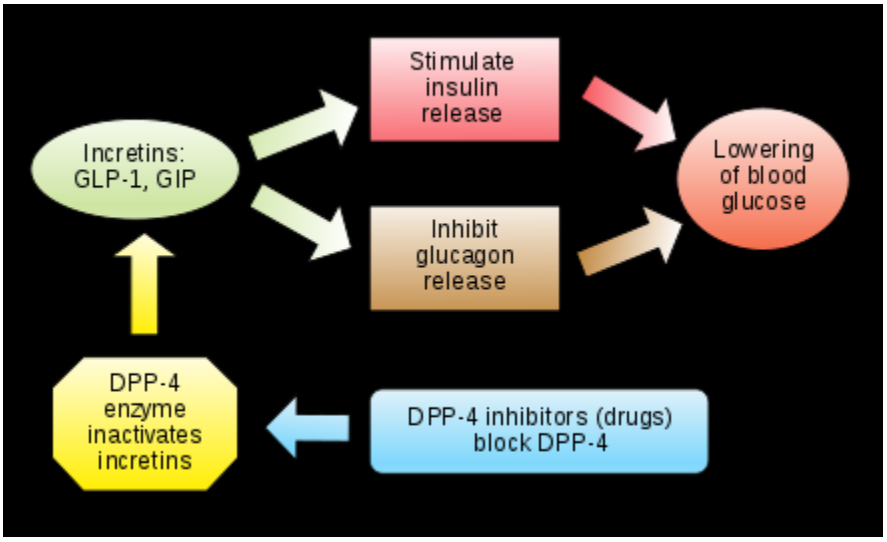
It has been shown that long-term subcutaneous administration of GLP-1 to patients with type 2 diabetes (for 6 weeks) improved the function of b-cells, reduced the level of glucose and glycosylated hemoglobin (HbA1c), and increased peripheral insulin sensitivity; in addition, a decrease in body weight of patients has been recorded.

However, as already noted, the period of circulation of endogenous or exogenous GLP-1 in the blood is extremely short (3-6 minutes) due to the rapid inactivation of incretins under the action of the dipeptidyl peptidase-4 enzyme.

Therefore, the use of DPP4 inhibitors to prevent the rapid breakdown of GLP1 has opened up an additional opportunity in the treatment of type 2 diabetes.

DPP4 is an enzyme that hydrolyzes incretins in the blood.

Thus, the mechanism of action of iDPP4 is based on an increase in the activity of incretins-GLP1.



Sitagliptin is the 1st drug from the group of iDPP4.

Sitagliptin inhibits DPP4 by 91.7%.

As noted earlier, iDPP4 contributes to an increase in the level of incretins in the blood. Incretins, in turn, stimulate the function of pancreatic beta cells.

Stimulation of Beta cells stops when normoglycemia is reached.

iDPP4 are used to correct carbohydrate metabolism in patients with type 2 diabetes. They can improve glycemic control by increasing endogenous insulin levels.

DPP4i have been found to reduce the risk of serious cardiovascular complications compared to other antidiabetic drugs. However, studies have been limited by their short duration of action, often <6 months.

Drugs iDPP4 by suppressing the activity of the enzyme DPP4 increase the concentration of GLP1, which is secreted in the intestine in response to food intake.

Vildagliptin (Galvus) is included among the iDPP4 and recommended by the FDA (USA) and EC for the treatment of type 2 diabetes, both as monotherapy and in combination with Metformin.

iDPP4 are not prescribed for impaired liver function, pregnancy, lactation, persons under 18 years of age.

One of the modern and well-studied drugs is Galus, since more than 22 thousand patients participated in the program (more than 70 randomized trials) to study its clinical efficacy, of which more than 14 thousand took Galvus

With the appointment of Galvus in Loza 100 mg / day for 24 weeks, a decrease in HbA1c levels has been noted from 0.6% with an initial HbA1c level of 8% to 1.9% with an HbA1c level of> 10%.

Also, the level of HbA1c decreased by an average of 1% both in patients with type 2 diabetes with normal body weight without obesity, and in those examined with a BMI> 35 kg/m2

For patients with HbA1c in the range of 7.6-9.0%, who have more stringent individual targets for glycemic control, achieving these goals by prescribing monotherapy is not possible. In this situation, immediately from the moment of diagnosing DM2, it is most appropriate to prescribe a combination of 2 hypoglycemic drugs that affect different mechanisms of the development of the disease.

The most common rational combinations include combinations of metformin (the basic drug that reduces insulin resistance) and drugs that stimulate insulin secretion: iDPP-4, SitaMet, GalvusMet, Janumet), which allows you to influence the pathogenetic mechanisms of type 2 diabetes (insulin resistance, secretory response of beta cells and hyperproduction of glucose liver).

In the course of international clinical trials involving over 22 thousand patients with type 2 diabetes, the effectiveness of Vildagliptin has been shown when used both as monotherapy and in combination with other hypoglycemic drugs.

The advantage of these drugs is the possibility of their use in groups of elderly patients, patients with hypertension and impaired renal function of moderate severity, patients of the cardiovascular risk group.

DPP4i are better tolerated, do not cause gastrointestinal disturbances, and are not limited when used in individuals with hypoxic conditions of various etiologies.

Due to their positive properties and clinical advantages, iDPP4 are being increasingly used in domestic clinical practice every year.

DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, linagliptin, alogliptin) - a group of oral incretin drugs do not cause hypoglycemia and weight gain.

Presumably (proven in animal experiments), these drugs have an additional advantage in maintaining the mass of pancreatic β-cells.

It is preferable to prescribe to patients with excess body weight or obesity, elderly people with a high risk of hypoglycemia.

In 2013, large randomized trials of SAVOR and EXAMINE were completed, which generally showed the cardiovascular safety of the use of DPP-4 inhibitors.

However, this should take into account the results of the SAVOR study, indicating the need for caution in people with heart failure.

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors are a new class of oral antidiabetic drugs that reduce glycemic levels independent of insulin and beta-cell function.

SGLT2 inhibitors, due to the unique mechanism of action that does not depend on the severity of insulin resistance and beta-cell deficiency, are equally effective both in patients with type 2 diabetes with a disease duration of less than one year and in patients with type 2 diabetes of a long course (more than ten years).

All inhibitors are highly selective for SGLT2 over SGLT1.

The safety of these drugs is due to an extremely narrow spectrum of action - the inhibition of a specific protein, which is present almost exclusively in the epithelial cells of the proximal tubules of the nephron.

Sodium-glucose cotransporter type 2 inhibitors

The introduction of this fundamentally new class of hypoglycemic agents into clinical practice is one of the important factors that necessitated an update of the 2011 Consensus.

The therapeutic potential to reduce HbA1c of this group of drugs is 0.8-0.9%.

The drugs and SGLT2 reduce the reabsorption of glucose in the kidneys and increase the excretion of glucose in the urine up to 60–80 g/day. The mechanism of action of SGLT-2 is also insulin-independent; therefore, they not only have a low risk of developing hypoglycemia, but can also be used for any duration of the disease, including against the background of a significant decrease in insulin secretion.

Additional benefits of this group are moderate weight loss (about 2 kg on average) and lower blood pressure (2–4 mmHg systolic, 1–2 mmHg diastolic).

Clinical studies have shown a trend towards a decrease in the level of uric acid in the blood plasma and a decrease in albuminuria (although these data require further study). Taking into account the peculiarities of the mechanism of action, they can be combined with all major classes of hypoglycemic drugs, which is reflected in the updated recommendations for the treatment of T2DM by leading international professional associations (however, the combination of both SGLT-2 and aGLP-1 remains unexplored).

The current update of the consensus algorithm of initiation and intensification of the antihyperglicemic therapy in treatment of the patients with type 2 diabetes mellitus (2015) is based on the preliminary document issued by the Russian Association of the Endocrinologists in 2011.

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