Peroral antidiabetics

Oral antidiabetic drugs (PADs) are drugs used in the treatment of diabetes mellitus. Their mechanism of action is dependent on the production of endogenous insulin and therefore **cannot be used in patients with type 1 diabetes**.

According to the site of action, PAD can be divided into 4 groups:

- **insulin sensitizers** - increase the sensitivity of cells to insulinu (biguanides), thiazolidinediones;
- **insulin secretagogues** - increase insulin release from β-cells of the pancreatic duct (sulfonylurea derivatives, glinides);
- **Intestinal glucosidase inhibitors** - reduce glucose absorption from the intestine - α-glucosidase inhibitors;
- **Inhibitors of glucose reabsorption in the proximal tubule** - increase glycosuria (glyphosates).

Insulin sensitizers

Increase the sensitivity of cells to insulin. They do not induce hypoglycaemia and are therefore referred to as **euglycaemic drugs**.

Biguanides

Metformin is now a basic PAD. It is well tolerated, and can be preferably combined with other antidiabetic drugs. It reduces cardiovascular mortality independent of diabetes compensation and has positive late effects of treatment (treatment can be started as early as prediabetes). It does not cause weight gain (unlike secretagogues and thiazolidinediones), so it is beneficial even for obese patients.[1] It is an inexpensive drug with no prescribing restrictions.

Mechanism of action

Increase the sensitivity of tissues (especially liver and skeletal muscle) to insulin and lower glycemia:

- by promoting glucose utilization in skeletal muscle and adipose tissue (by stimulating glycolysis),
- by inhibiting gluconeogenesis in the liver.
- reducing glucose resorption from the gut.

Side effects

Stimulate glycolysis and thus lactateu formation. Thus, a serious complication may be ***lactate acidosis***. Individuals with renal failure, cardiopulmonary insufficiency, hepatic insufficiency (alcoholics) are predisposed to this. In these cases, biguanides are contraindicated. *Gastrointestinal distress* may occur early in treatment. Intravenous administration of iodine contrast agent may lead to **renal failure**. This may induce accumulation and increase the risk of lactic acidosis. The use of biguanides must therefore be discontinued 48 hours before the examination. They are also discontinued before surgery.[2] They are not recommended for the treatment of diabetes during pregnancy. Insulin should be used to maintain blood sugar levels to minimize the risk of fetal malformation.

Thiazolidinediones

Mechanism of action

They have similar effects to biguanides. They activate the transcription of genes responsible for carbohydrate and fat metabolism via the nuclear receptor PPAR-γ.

Side effects

They cause mild fluid retention (hence diuretics are sometimes added), so they are not administered in patients with heart failure, edematous conditions, pregnancy. Pioglitazone is contraindicated in haematuria of uncertain origin. Require periodic monitoring of liver tests. There is often weight gain (fluid retention, increase in adipose tissue). An eye examination is also advisable before deployment, because of the risk of worsening diabetic macular oedema.

Today, only one agent **pioglitazone** is used (rosiglitazone has no beneficial effect on cardiovascular mortality and is currently withdrawn from the market[3]), is well tolerated, and is suitable for metformin contraindication.

Insulin secretagogue

They increase insulin release from the β-cells of the pancreas. They are risky in terms of possibly inducing **hypoglycemia** and causing **weight gain**.

Sulphonylurea derivatives

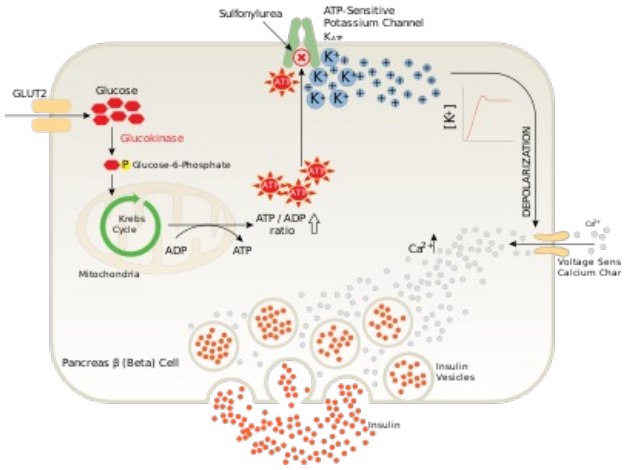
Mechanism of action

Increased insulin release from pancreatic β-cells is achieved by blockade of ATP-sensitive < sup>+ < / sup> channels in the membrane. This will reduce the flow of potassium from the cell, depolarization of the membrane and the opening of Ca^{2+} channels will occur. The ingress of Ca^{2+} ions causes insulin to be released

Side effects

Hypoglycaemia can be the most serious complication, especially with longer-acting agents. This group of drugs also increases appetite, so treatment is usually associated with weight gain.

Generation II (*glipizide* ***and generation III (***glimepiride) **drugs are used in practice. Most commonly in combination therapy with metformin (especially when type II DM is not adequately compensated by metformin monotherapy).**



Mechanism of action of sulfonylureas

Glinides

Newer drugs also "'block ATP-sensitive to^{+} channel "' in β-cell membranes. They act quickly, so they are ideal to take with food to compensate for postprandial hyperglycemia. Examples of substances are "'repaglinide" and "'nateglinide".

Intestinal glucosidase inhibitors

They are used to control postprandial hyperglycaemia. The basic substance used in this group is "'acarbose".

Mechanism of action

By inhibiting enzymes, they restrict and slow the absorption of carbohydrates in the small intestine. The blocked enzyme does not cleave them and thus they cannot be resorbed (absorption of monosaccharides remains unchanged).

Side effects Flatulence, diarrhoea and abdominal pain caused by the action of the microbial gut flora on undigested complex carbohydrates.

If the patient develops hypoglycaemia due to other drugs, it cannot be treated orally with sucrose but only with glucose.

Glyphosates

Mechanism of action Inhibit the SGLT-2 transporter in the proximal tubule of the nephron, thereby blocking glucose reabsorption and increasing glycosuria. Thus, the renal threshold for glucose is shifted and glycaemia is reduced. Increased glucose losses lead to loss of energy and weight loss in the patient. They also decrease glycated hemoglobin, uricemia, slightly increase HDL cholesterol and due to osmotic diuresis there is a slight decrease in blood pressure.

Side effects Increase in frequency of urogenital tract infections. Most often these are mycotic infections in women. Because of increased diuresis, caution is in order in patients at risk of hypotension or volume depletion.

The risk of hypoglycaemia is minimal with glyphosate treatment.

In the Czech Republic are available **dapagliflozin**, **kanagliflozin** and **empagliflozin**.

Empangliflozin in combination with metformin for oral use

Incredibles

Novel agents modulating the effects of incretins[4]. They are very effective, safe, but expensive. They increase insulin secretion, inhibit glucagon, and act only in hyperglycemia.

Exenatide is a synthetic analogue of GLP-1 (glucagon-like peptide 1), incretin analogue. It is applied s. c., thus it is not a PAD.

Dipeptidyl peptidase 4 inhibitors (DPP-4) block an enzyme that inactivates endogenous incretins. They are less effective than incretin analogues but are cheaper and can be administered orally. Example substances: **sitagliptin**.

Comparison of therapeutic options

The strategy for treating type 2 diabetes mellitus with oral antidiabetic agents depends, among other things, **on the patient's comorbidities** - the most considered **cardiovascular risk**' renal insufficiency'**. Cardiovascular risk can be assessed using the ASCVD SCORE table, and the presence of heart failure is also assessed. If the patient does not have these comorbidities, the therapy is selected according to other goals individually, e.g. elimination of hypoglycaemic episodes, weight loss, more favourable price. Conclusion of the therapy is written in the following scheme.**

The following scheme summarizes each PAD and their advantages and disadvantages.

Pharmacum	Advantages	Side effects, contraindications
Metformin	Initial therapy	gastrointestinal disorders, lactic acidosis, KI in renal insufficiency
Sulfonylurea	potent drug	weight gain, hypoglycemia
GLP-1 agonists	reduction of CVD risk, weight reduction	gastrointestinal problems, need for injections, high cost
Thiazolidinediones	pioglitazone: modification of lipid spectrum, lower CVD risk	fluid retention, weight gain, risk of bladder cancer (pioglitazone)
Glinid	potent drug	weight gain, hypoglycemia, must be taken 3 times a day
Inhibitor SGLT-2	weight loss, blood pressure reduction, improved cardiovascular and renal prognosis	vaginal candidiasis, urinary tract infections, fracture risk, amputation risk
Inhibitor DPP-4	weight neutral	high price
Alpha-glucosidase inhibitor	weight neutral	frequent gastrointestinal problems, dosage 3 times a day

Links

Related articles

- Diabetes mellitus
- Type 2 diabetes mellitus
- Insulin therapy
- Incretin analogues
- Insulin therapy
- Insulin resistance

External links

- Přítup k volbě léků u diabetu 2. typu (https://diabetologia-journal.org/2018/10/05/new-easd-ada-consensus-guidelines-on-managing-hyperglycaemia-in-type-2-diabetes-launched-at-easd-meeting-new-recommendations-include-specific-drug-classes-for-some-patients-and-enhancing-medication-a/)

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