Hypolipidemics

Hypolipidemics are pharmacological products used for the treatment of **hyperlipoproteinemia.**

Lipoproteins

Lipids are transported in the blood through macromolecular complexes - **lipoproteins** only short-chain fatty acids are able to bind to albumin). Several species can be distinguished according to density - **chylomicrons, VLDL, LDL, HDL and IDL.** They have a similar structure - the core is made up of hydrophobic substances, ie cholesterol esters and triacylglycerols (TAG), which are coated with a layer of non-esterified cholesterol, phospholipids and a carrier protein (apoprotein). They differ in the amount and ratio of TAG and cholesterol and the type of apoprotein.

Chylomicrons

They are synthesized in the gut. Their main function is to transport food-borne TAGs. Through the ductus thoracicus, they bypass the liver and enter the systemic circulation directly. As they progress through the circulation, TAGs are released from them in the tissues in the presence of lipoprotein lipase. At the same time, they deliver some of their HDL apoproteins. Residues of chilomicrons are taken up by the liver.

VLDL (very low density lipoproteins)

Primarily synthesized in the liver, they transport TAGs to peripheral tissues, where they are released by lipoprotein lipase (identical mechanism to chilomikers). The resulting free fatty acids are either stored in adipose tissue or metabolically utilized (myocardium, skeletal muscles).

LDL (low density lipoproteins)

They are formed in the bloodstream from VLDL. Their main components are cholesterol esters, ie substances important in the origin and development of atherosclerosis. LDLs are taken up in tissues (from a physiological and pathophysiological point of view, the liver is the most important) depending on the presence of a specific LDL receptor. In the liver, esters are hydrolyzed to free cholesterol, which is used to synthesize membrane components or bile acids. In addition to this external supply, cholesterol is also synthesized de novo in the liver. HMG-CoA reductase is important in this process (its activity can be therapeutically affected).

HDL (high density lipoproteins)

They bind cholesterol, which is obtained by extraction from peripheral tissues. This explains the beneficial effect of these particles in slowing down atherogenesis.

Dyslipoproteinemia and Their Classification

> They are pathophysiological units characterized by an altered spectrum of lipids in the systemic circulation. They are detected from a serum sample taken after a 10-hour fast. From the point of view of atherogenesis, the assessment of cholesterol, LDL, HDL levels and the mutual LDL / HDL ratio, the so-called **atherogenic index,** is particularly important. TAG levels should not exceed 5-15 mg / l. **When deciding on treatment, it is advantageous to distinguish whether it is**

1. **primary hypertriglyceridemia**;
   - alcohol, TAG, carbohydrates, estrogens should be excluded from the diet; weight reduction, increase the intake of omega-3 unsaturated fatty acids
   - medicated: fibrates, nicotinic acid
2. **primary hypercholesterolemia**;
   - cholesterol intake, high fiber diet, complex sugars and unsaturated MK, weight reduction;
   - drug: PSCK9 inhibitors, HMG-CoA reductase inhibitors (statins), ion exchangers, nicotinic acid;
3. **lack of HDL**;
   - it often occurs in the presence of high levels of TAGs, so it is necessary to normalize their amount; nicotinic acid administration directly increases HDL levels;
4. **secondary hyperlipoproteinemia**;
   - treatment of the cause + symptomatically according to the finding in the blood.

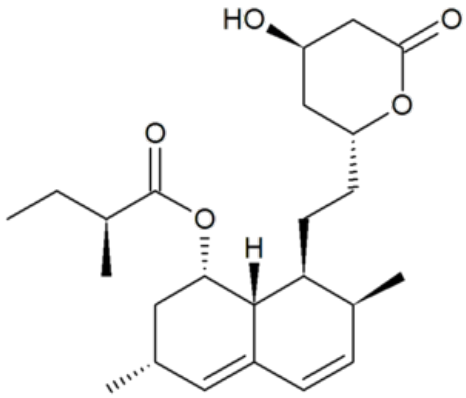
Classification of Hypolipidemics

1. **PCSK9 inhibitors**
2. **Statins**,
3. **Fibrates,**
4. **Sterol transporter blockers**
5. **Ion exchangers,**
6. **Nicotinic acid**

Statines

Statins are competitive inhibitors of HMG-CoA reductase. HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase is an enzyme that catalyzes the major step in cholesterol synthesis, the conversion of HMG-CoA to mevalonic acid. Its inhibition reduces intrahepatic cholesterol synthesis, which leads to an increase in the number of LDL-receptors on hepatocytes, increased uptake of LDL by the liver and thus a decrease in circulating blood cholesterol.

Another effect of statins is inhibition of smooth muscle cell proliferation in the vessel wall, improvement of endothelial cell function, stabilization of the atherosclerotic plaque, it also has antiplatelet and anti-inflammatory effects.



Lovastatin.

Pharmacokinetics

About 30% of the administered dose is absorbed from the intestine, statins are taken up by the liver, where they are metabolized and then excreted by the bile.

Indications

The main indication for statin therapy is the treatment of hypercholesterolemia, as well as the achievement of target LDL cholesterol levels in high-risk patients with normocholesterolemic. They are used in the treatment of familial hypercholesterolemia type IIa. With statin therapy, up to a 40% reduction in LDL-cholesterol levels can be achieved (in combination with ion exchangers) up to 60%

Contraindications

Pregnancy, lactation, childhood.

Side Effects

Currently, there is a growing body of knowledge about the side effects of statins. It is likely that the frequency of already known side effects is higher than previously thought and that there are also previously unknown side effects. Previous studies have focused primarily on demonstrating a reduction in cardiovascular morbidity and overall mortality. However, they did not focus so much on identifying side effects. It should also be noted that many studies conducted in the past have ruled out up to 30% of patients in the pre-randomization phase due to comorbidities and concomitant medications!

According to some studies, statin treatment significantly reduces coenzyme Q10 (cholesterol is a precursor of CoQ10), which may be a factor in some of the side effects listed below (myopathy, rhabdomyolysis, neuropathy) - probably due to damage to membrane structure.

- Increase of aminotransferase activity and creatine kinase.
- myalgia;
- severe skeletal muscle myopathy with pain, high creatine kinase activity and hyperkalemia; necessary interruption of therapy, otherwise the possibility of transition to rhabdomyolysis with myoglobinuria and renal failure - these conditions may rarely occur in monotherapy, the much higher incidence is reported in combination with CYP3A4 inhibitors (erythromycin, SSRI, azole antifungals, fibrates, cyclosporine);
- tendinitis, tendon ruptures (t. Achillei, m. quadriceps, m. biceps femoris);
- sleep disorders (up to 10 %?);
- cataract;
- bleeding into CNS,
- increased risk of DM.

Some professional societies recommend substituting coenzyme Q10 for statins due to the above findings. Especially with long-term therapy, in the event of an emergency or with an increased risk of cellular damage.

Examples (according to increasing hypolipidemic efficacy)

- pravastatine tbl.10 a 20 mg,
- lovastatine,
- fluvastatine (ve formě s prodlouženým účinkem),
- simvastatine tbl. 10–40 mg,
- atorvastatine tbl. 10, 20 a 40 mg,
- rosuvastatine tbl. 10, 20 a 40 mg.

Fibrates

Fibrates are derivatives of fibric acid. They increase lipoprotein lipase activity and block lipolysis intracellularly. The result is a reduction in circulating VLDL (TAG). The amount of HDL also increases slightly (a decrease in TAG frees up the HDL capacity for cholesterol ester binding). They are used to treat hypertriglyceridemia.

Side effects

The most common side effects include nausea, vomiting and skin rashes. Rarely, myopathy (up to rhabdomyolysis) and arrhythmias may also occur. The risk is increased when HMG-CoA reductase inhibitors are co-administered.

Examples

- fenofibrate,
- clofibrate,
- bezafibrate,
- gemfibrozil,
- ciprofibrate

Sterol Transfer Blockers

Ezetimibe belongs to a new class of hypolipidemic. It blocks the sterol transporter, the Niemann-Pick C1-Like 1 protein (NPC1L1), which is essential for the absorption of cholesterol and phytosterols in the gut.

Indication

Ezetimibe is co-administered with a statine:

- in primary hypercholesterolaemia (non-familial or heterozygous familial) as a dietary supplement, if statin therapy alone is not sufficient; in homozygous familial hypercholesterolemia

The following is used in monotherapy:

- in primary hypercholesterolaemia (non-familial or heterozygous familial) as a dietary supplement, if statin treatment is contraindicated or not tolerated;
- in homozygous familial sitosterolemia as a dietary supplement. primární hypercholesterolemii (nefamiliární nebo heterozygotní familiární) jako doplněk diety, pokud je léčba statinem kontraindikována nebo není tolerována;

Ionchangers

They are insoluble macromolecular resins that bind bile acids (cholesterol metabolites) in the intestinal lumen and prevent their re-absorption.

Under normal circumstances, about 95% of the excreted bile acids return to the liver (enterohepatic circulation).

Decreased return after ion exchange administration leads to increased bile acid synthesis from cholesterol. This results in increased uptake of LDL by the liver and mobilization of cholesterol from the tissues.

Side Effects

- Constipation, bloating (it is, therefore, advisable to supplement the diet with foods rich in fibre),
- rarely malabsorption of vitamin K,
- dry, peeling skin
- the absorption of some drugs may be impaired (cardiotonic, thiazide diuretics, warfarin, some NSAIDs - it is advisable to administer this drug at least one hour before the application of the ion exchanger).

Examples

- Cholestyramine.
- Colestipol.

Nicotinic acid

Nicotinic acid (niacin, vitamin B3) and its derivatives are used to treat hyperlipidemias. It inhibits VLDL secretion from the liver and increases peripheral lipoprotein lipase activity. Subsequently, there is a reduction in circulating VLDL (ie TAG) and subsequently LDL (cholesterol). In adipose tissue, on the other hand, it reduces the release of MK from stores by inhibiting intracellular lipase, which further reduces TAG delivery to the liver and VLDL synthesis.

Side Effects

- harmless vasodilation (mediated by the release of prostaglandins) in the cutaneous bed associated with subjective feelings of heat - can be managed by administration of acylpyrin,
- in 1/5 treated hyperuricaemia,
- rash.

References

Related Articles

- Lipoproteins
- Hypolipidemic treatment
- Obesity
- Lipid metabolism disorders

Source

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