**Metabolic drugs in anti-ischemic therapy**

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Cardiovascular diseases are considered the most common precondition of death in gerontоlogy. As the population of the most developed countries continues to grow, the importance of aging increases as a risk for all cardiovascular diseases. Despite the success of recent decades in the prevention and treatment of coronary heart disease, the optimization of treatment of this disease remains the leading aim among the acute problems of progressive cardiology. For a long time, the anti-ischemic efficacy of metabolic therapy was rejected, and the treatment of coronary heart disease (IHD) was considered only on the basis of beliefs for improving hemodynamics. The result of traditional treatment was primarily aimed at reducing oxygen demand in the myocardium. But substances that affect the hemodynamic characteristics are effective, mainly when it comes to preventing angina attacks. Although it practically doesn`t protect the myocardial cell from metabolic configurations. As known, the usual ratio between the delivery of oxygen to cardiomyocytes and the need for it is considered a clear ratio, which provides the usual metabolism. Under normal conditions, free fatty acids serve as the main substrates for generating energy in cardiomyocytes, the oxidation of which provides 60-80% of adenosine triphosphate synthesis, and glucose.

In this regard, drugs, which stabilize the metabolism of the myocardium, should be an obligatory component of IHD therapy.  There are two main directions of metabolic therapy for myocardial diseases:

• Optimization of the processes of formation and consumption of energy;

• Normalization of the balance between the intensity of free radical oxidation and antioxidant protection.

The first drugs, which were designed to improve the state of myocardial energy exchange in diseases of the cardiovascular system, were drugs that promoted anabolism of macroergic compounds. Traditionally, this group includes vitamins of group B (especially B1, B6, B12, etc.), Inosine (riboxine), inositol (also considered a vitamin of group B). At a certain stage in the development of medical science, these drugs were quite popular, but the experience of their clinical application showed low effectiveness of such therapy. First of all, the failure was associated with the pharmacological unfounded use of this class of drugs. It`s obvious that the introduction of adenosine triphosphate externally doesn`t matter, cause this macroerg is formed in the body in incomparably large quantities.

The last stage of metabolic therapy was the creation of trimetazidine, a product that blocks the oxidation of free fatty acids under hypoxic conditions. The decrease in the oxidation of fatty acids with trimetazidine has a beneficial effect on the metabolism of the ischemic myocardium, since the creation of energy is enhanced by the oxidation of glucose. This is much more successful than using oxygen. In addition, glucose is not metabolized to lactate. The cytoprotective effect of trimetazidine is based on these two mechanisms. Now this product is well known and used in medical practice. A recent meta-analysis of 12 clinical trials of trimetazidine demonstrated a significant reduction in cases of angina attacks in patients with stable angina. Cardioprotective characteristics of this product, among other things, are proven in acute myocardial infarction, percutaneous angioplasty, and shunting of the coronary artery. The experience of using trimetazidine, mildronate and ranalazine confirmed the probability of achieving an anti-ischemic result. The intensity of β-oxidation of free fatty acids decreases, and aerobic glycolysis is incompatible due to the preservation of the hypoxic state.

The second direction of creating substances with metabolic action is activation of glucose metabolism. The advanced adherents of this class of metabolic modulators are ranolazine and etomoxir. A partial inhibitor of fatty acid oxidation, ranolazine demonstrated higher anti-ischemic activity in patients with stable angina in the form of monotherapy (MARISA trial) and in combination with a β-blocker (CARISA study). The experience of using trimetazidine, mildronate and ranalazine confirmed the possibility of achievement an anti-ischemic effect. The intensity of β-oxidation of free fatty acids decreases and aerobic glycolysis is incompatible due to the preservation of the hypoxic state. Participation of free radicals has been proven in cardiovascular pathology. Activation of peroxidation processes is caused by frequent anginal attacks, which cause hypercatecholaminemia and stimulation of lipolysis. Because of hypoxia (ischemia) in mitochondria, cardiomyocytes are violated. As a result, intermediate metabolites of the Krebs cycle accumulate, which can easily be reduced to free radicals and peroxide compounds that suppress antioxidant defense systems. The result is a paradoxical situation – the oxygen content decreases in the cell, which leads to increase of oxygen radicals.   
This phenomenon is called oxidative stress. This is especially important in elderly patients. The pathogenetic mechanism of the progression of IHD and the development of its complications is associated with the activation of free radical oxidation. In this regard, therapy with metabolic drugs in this category should be combined with the appointment of drugs that have an antioxidant effect.   
The main groups of drugs those are able to withstand oxidative stress:

• Antioxidant agents that inactivate free radicals and prevent their formation;

• Drugs involved in the restoration of antioxidants;

• Drugs that are mediated by antioxidant activity.

It should be noted that antioxidants are rarely included in the treatment of patients with coronary atherosclerosis. Insufficient popularity and lack of traditions of their wide application is largely due to the lack of effective medicines, that have antioxidant activity and able to quickly reduce the effects of oxidative stress. Real dosage forms, unfortunately, exist only for vitamins. Widely are used C and E. The attitude to these drugs in doctors is very ambiguous. On the one hand, the pathogenetic conditionality of using this class of drugs in IHD isn`t doubt and, on the other hand, it wasn`t possible to prove their effectiveness.

A promising area of pharmacological search for new anti-ischemic agents is the creation of dosage forms that have anti-ischemic, metabolic and antioxidant activity with minimal side effects. In the form of a pharmacological agent, the domestic pharmaceutical industry is able to offer tiotriazoline, a product with a metabolic and antioxidant effect. The anti-ischemic effect of this drug is based on the ability to enhance the compensatory activation of anaerobic glycolysis, to reduce the inhibition of oxidative processes in the Krebs cycle while maintaining the intracellular adenosine triphosphate pool and to stabilize the metabolism of cardiomyocytes.

At the same time, thiotriazoline activates the antioxidant system of enzymes and inhibits the processes of lipid peroxidation in ischemic areas of the myocardium. Thiotriazoline activates antiradical enzymes, contributes the economization of the consumption of tocopherol. The drug inhibits the formation of the initial and final products of the lipid peroxidation reaction in pathologically altered tissues. It protects the structural and functional integrity of the cardiomyocyte membranes, and also reduces myocardial sensitivity by adrenergic cardiostimulatory effects of catecholamines and prevents progressive inhibition of myocardial contractile function. Thiotriazoline increases the resistance of cardiomyocytes to hypoxia.

Based on the results of the treadmill test, thiotriazoline significantly increased the duration of the load and the maximum achievable heart rate at the peak of the load, and also it reduced the overall average level of displacement of the ST segment and the level of systolic blood pressure. There are several differences between thiotriazoline and riboxinе. Riboxinе has a lesser effect on the cumulative shift level of the ST segment and the maximum heart rate and does not affect the level of hypertension. Acquired data are indicated that thiotriazoline has the correct anti-ischemic effect, and myocardial contraction becomes the most economical. The results of the stress test were confirmed by data from a 24-hour ECG monitoring, according to which in the future thiotriazoline there was a significant reduction in the time of myocardial ischemia and the duration of individual episodes of ischemia.

In conclusion, the first drugs for anti-ischemic therapy were vitamins of group B, but their effectiveness was refuted in clinical trials. The next drug was trimetazidine, since it has a high cytoprotective effect. This drug is especially effective in patients with stable angina. But thiotriazoline is a new anti-ischemic drug that includes anti-ischemic, metabolic and antioxidant activity with minimal side effects. Summing up, given the good tolerability, efficacy and safety, thiotriazoline can be recommended as a remedy of metabolic therapy for the treatment of IHD in the elderly.

Literature:

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