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Metabolic cardiocytoprotectors (*trimetazidine and trimethylhydrazine*) in geriatrics

Short review

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Abstract. The review presents the clinical studies results of the effectiveness of cardiocytoprotectors, fatty acids synthesis inhibitors, trimetazidine (preductal), and trimethylhydrazine (meldonium, mildronate) in the treatment of cardiovascular disease (angina pectoris, chronic heart failure) and the central nervous system disease (dyscirculatory encephalopathy, chronic cerebral insufficiency, stroke) various ages patients. These data indicate the prospects of using these drugs in the complex therapy of cardiovascular and cerebrovascular diseases in the geriatric clinic.

Keywords: metabolic cardiocytoprotectors, cardiovascular and cerebrovascular pathology, trimethylhydrazine, elderly

The incidence of the elderly is characterized by high levels of cardiovascular and cerebrovascular pathology. There are age-related structural, metabolic, and functional changes in the body: hypoxia, energy deficiency, oxidative stress, and vascular endothelial disorders.

In the complex therapy of metabolic disease patients, the use of myocardial cytoprotectors is promising. Myocardial cytoprotectors do not affect hemodynamics; and directly affect cardiomyocytes and vascular endothelial cells at the cellular level, correct energy, and metabolic disorders in the myocardium, optimize the energy formation and expenditure, normalize the balance between free radical oxidation and antioxidant processes, and support the contractile myocardium ability [6-9].

The main direction of myocardial cytoprotection is the bioenergetic processes optimization in the ischemic myocardium. Myocardium energy supply is based on the synthesis of ATP by phosphorylation of two main substrates - free fatty acids and glucose. Myocardial ischemia disrupts the energy metabolism of cardiomyocytes, reduces the intensity of glucose oxidation, and increases the use of free fatty acids as an energy source. An imbalance between the oxidation of glucose and free fatty acids leads to a decrease in ATP production, intensification of peroxidation processes, violation of cellular homeostasis of cardiomyocytes, and reduced myocardial contractility [10, 11].

Cytoprotectors switch the ischemic myocardium metabolism from fatty acid oxidation to a more economical pathway of anaerobic glucose oxidation (glycolysis), which reduces myocardial oxygen demand and increases the cardiomyocyte's resistance to ischemia. As a result of increased glucose oxidation and increased ATP synthesis, the oxidation of free fatty acids is inhibited, the free radicals formation is reduced, intracellular acidosis is reduced, and vascular endothelium condition is improved. Therefore, the use of agents that block the oxidation of the fatty acids and stimulate glucose oxidation on an alternative basis, is a promising area of myocardial cytoprotection [12, 13].

A lot of clinical studies indicate the effectiveness of the use in complex therapy of cardiovascular diseases of myocardial cytoprotectors, partial inhibitors of fatty acid oxidation. The stench galvanizes the oxidation of fatty acids with a path of partial inhibition of the oxidation of free fatty acids in mitochondria (trimetazidine) or intermediates their transport through the cell membrane (trimethylhydrazine).

Trimetazidine (preductal) - (1-[2, 3, 4 trimethoxybenzyl]) piperazine dihydrochloride) inhibits the activity of 3-ketoacyl-CoA-thiolase in mitochondria, which is an enzyme for the oxidation of free fatty acids. This helps to unlock pyruvate dehydrogenase and switch myocardial energy metabolism to glycolysis. As a result, the metabolism of membrane phospholipids improves, and phosphorylation increases. This reduces the production of free radicals, reduces the passive permeability of membranes, as well as increases their resistance to hypoxic damage, and improves the vascular endothelium condition [14, 15]. The positive effect of trimetazidine on cardiomyocytes and endothelial cells is manifested in the reduction of mechanical and endothelial dysfunction, which is characteristic of ischemia and heart failure. This protects the myocardium from necrosis and apoptosis [16, 17].

Trimetazidine reduces myocardial ischemia in the early stages of its development (at the level of metabolic disorders), which prevents the occurrence of later manifestations, such as angina, decreased heart rate, and cardiac arrhythmia [18].

The safety and efficacy of trimetazidine in the treatment of cardiovascular disease have been proven by a number of controlled clinical studies.

The efficacy of trimetazidine in patients with coronary heart disease has been established in clinical studies. The drug increased the tolerance of patients to physical activity, increased the threshold of ischemia (according to exercise tests), and reduced the number of anginal attacks [19-23].

Trimetazidine is widely used in the treatment of patients with stable angina pectoris, increasing the effectiveness of treatment. The inclusion of trimetazidine in antianginal therapy after 12 weeks of treatment reduced the frequency of angina attacks and the number of short-acting nitrates, increased the duration of exercise tests, and improved quality of life [24-28].

Data from meta-analyses of randomized placebo-controlled clinical trials have shown a higher efficacy of trimetazidine compared with other antianginal drugs in the treatment of stable angina [29].

Trimetazidine can significantly reduce overall mortality and the development of serious cardiovascular complications in acute myocardial infarction patients and coronary heart disease patients after myocardial infarction compared with patients receiving only standard therapy [30, 31].

Clinical studies have shown that trimetazidine in cardiovascular insufficiency patients of functional class II-III has a positive effect on clinical and hemodynamic status: reduces shortness of breath, and increases the ejection fraction of the left ventricle [32]. The effectiveness of trimetazidine in the treatment of chronic heart failure in coronary heart disease patients has been established in clinical studies [33].

Myocardial cytoprotectant trimetazidine, optimizing energy metabolism in the myocardium, does not cause negative isotropic and chronotropic effects. This determines the feasibility of its use in the treatment of patients of older age groups.

High efficacy and good tolerability of the drug in elderly and senile patients have been established in multicenter clinical studies.

Trimetazidine significantly increased the effectiveness of treatment, reduced the frequency of angina attacks, increased the duration of stress tests, improved electrocardiogram, and also had a positive effect on the quality of life in the treatment of elderly stable angina patients. [34-36].

Trimetazidine was likely to improve clinical performance and stress test parameters in patients 65-85 years of age after 4 weeks of myocardial infarction. No adverse reactions were observed with trimetazidine [37].

The positive effect of trimetazidine on the clinical course of the disease in elderly coronary heart disease patients and diabetes patients is shown in a clinical study [38].

Trimetazidine normalizes the daily dynamics of blood pressure due to its effect on vascular endothelium and improving the viscous properties of arteries in the complex therapy of elderly patients with coronary heart disease and hypertension, along with antianginal and antiischemic effects [39].

Trimetazidine significantly reduced the functional class of chronic heart failure, increased exercise tolerance and myocardial contractility, and improved the quality of life of such patients over 75 years of age [40].

Trimethylhydrazine (mildronate, meldonium) - (3- (2,2,2-trimethylhydrazine-propionate), blocks transport and reduces the accumulation in mitochondria of active forms of long- and short-chain free fatty acids, reduces the rate of their carotene-dependent β-oxidation and switches energy in cardiomyocytes from the oxidation of free fatty acids to anaerobic glycolysis, in which glucose is used as an energy source [41, 42].

Mildronate promotes the formation of γ-butyrobetaine by inhibiting the enzyme γ-butyrobetaine hydroxylase, which intensively induces the production of nitric oxide. Nitric oxide is one of the most effective endogenous antioxidants and endothelioprotectors, which determines the effects of mildronate, such as optimizing microcirculation, reducing peripheral vascular resistance, and reducing vascular spasm in the body, especially in the myocardium and brain [43, 44].

All this determines the effectiveness of mildronate in the complex therapy of cardiovascular and cerebrovascular diseases, as shown in clinical studies.

The inclusion of mildronate in standard antianginal therapy (beta-blockers and nitrates) improved both subjective (reduced the incidence of angina) and objective (reduced myocardial ischemia according to the test with a load on a bicycle ergometer) indicators, had a positive effect according to computed tomography), and reduced the need for short-acting subglinval nitrates in stable angina II-III functional class patients [45-48].

The inclusion of mildronate in the complex therapy of chronic heart failure patients increased contractile and pumping function of the left ventricle, increased endurance to stress, and decreased functional class of chronic heart failure [49].

Mildronate is an effective and safe treatment for patients with stable angina in combination with chronic heart failure II FC. As a result of a 20-day course of treatment, probable clinical improvement was observed in most patients [50].

Mildronate improves the energy potential of cardiomyocytes and reduces the process of structural remodelling of the myocardium, which determines its effectiveness in patients with cardiac arrhythmias, in particular, atrial fibrillation.

Mildronate has a positive effect on the course of arrhythmia in patients with coronary heart disease and ventricular arrhythmias. A decrease in the total number of ventricular arrhythmias (on average by 86%) and a decrease in the number of paired forms of ventricular arrhythmias by 90% is observed with the use of mildronate [51].

The effectiveness and safety of mildronate in patients with the cerebrovascular disease have been shown in a number of clinical studies.

Mildronate improves cerebral hemodynamics and subjective and objective neurological symptoms - reduces headache, improves performance, reduces asthenia, and improves cognitive function in disculative encephalopathy patients [52, 53].

The efficacy of mildronate in patients with ischemic stroke has been established in randomized placebo-controlled multicenter studies. The drug improves cerebral hemodynamics and restores brain function. Indicators of the electrical activity of the brain are optimized, and positive changes in cerebral hemodynamics are observed when taking mildronate.

The use of mildronate helped to improve higher brain functions (memory, attention), reduce exhaustion and increase the reactivity of nervous processes.

The drug promotes regression of general cerebral symptoms, and vestibular and speech disorders [54, 55, 56].

According to clinical studies, mildronate is an effective drug that is well tolerated in the elderly.

Mildronate as part of combination therapy in elderly stable angina II-IV functional class patients helped to reduce episodes of painful and painless myocardial ischemia. The number, duration, and intensity of anginal attacks during the day and the need for nitroglycerin decreased, and exercise tolerance increased in patients [57].

The effect of mildronate on oxidative processes and endothelial function in an open-label controlled study was studied in elderly coronary heart disease patients. Mildronate (500 mg/day for 12

weeks) was found to reduce the level of lipid peroxidation products in low-density mitochondria, increase the resistance of lipoproteins to oxidation, and increase the level of nitric oxide in the blood [58].

Mildronate is successfully used in the treatment of chronic heart failure in elderly patients. The inclusion of mildronate in the complex therapy of elderly chronic heart failure patients increased the clinical effectiveness of treatment, improved the general condition of the patient, and reduced the functional class of chronic heart failure [59, 60].

According to the literature, mildronate is effective in the treatment of cerebrovascular diseases in the elderly.

Mildronate improved cerebral hemodynamics, reduced headache, increased efficiency, and improved subjective and objective neurological symptoms in elderly ischemic brain injury patients after stroke [61].

Open randomized controlled trials have shown a positive effect of mildronate on cognitive function in elderly hypertension patients, and cognitive impairment patients. Course mildronate therapy contributed to the preservation of cognitive-mnestic functions, which was manifested by a decrease in memory and attention disorders, improving the overall cognitive status of patients [62, 63].

Age-related disorders of myocardial metabolism are an important prerequisite for the development of cardiovascular disease in the elderly. Metabolic cardiocytoprotectors, partial inhibitors of free fatty acid oxidation - trimetazidine (product) and trimethylhydrazine (mildronate, meldonium) optimize the energy supply and metabolism of cardiomyocytes. They have a pronounced cytoprotective, antioxidant and antianginal effect, reduce the severity of biochemical damage to cardiomyocytes, and hemodynamic effects of myocardial and cerebral ischemia. This determines the effectiveness of their use in the treatment of cardiovascular and cerebrovascular diseases in the elderly.

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