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Activities of the Combined Drug in Conditions of Alcoholic Intoxication

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Abstract: Recently, in connection with the spread of alcoholic cardiomyopathy among the working population of industrialized countries, an urgent need is to search for new drugs with a strictly directed action, taking into account the complex mechanisms of the damaging effect of ethyl alcohol on the myocardium. In this regard, the combined agent of L-arginine with thiotriazoline (developed by NPO Farmatron) is of interest. It has been experimentally proven that in terms of the strength of the cardioprotective effect (influence on the level of the ST2 marker in the myocardium of rats with alcoholic cardiomyopathy), the combined agent L-arginine/thiotriazoline significantly exceeds the reference preparations Mildronate and Mexidol.

Keywords: experimental alcoholic cardiomyopathy, L-arginine, thio-triazoline, mildronate, mexidol.

Relevance; Alcohol abuse is a serious medical and socio-economic problem. According to the World Health Organization, the number of patients with alcoholism in the 2000s reached 140 million [1]. Currently, alcohol consumption in the United States has decreased, while in the countries of the former USSR and Japan it has increased. Regular alcohol abuse leads to the development of alcoholic cardiomyopathy (ACMP), and this pathology is the cause of the development of a fatal complication, causing 1/5 of all cases of sudden cardiac death [2]. According to different authors, the prevalence of the disease ranges from 3.8% to 40% of all cardiomyopathies [3].

ACM is a specific dilated cardiomyopathy (ICD-142.6), which, both in pathogenesis and in the features of its clinical picture, differs significantly from other most common diseases of the cardiovascular system [4]. This is due to the fact that ACMP is based on non-coronary, non-inflammatory mono-etiological alcohol-induced toxic damage to the heart muscle, the fine mechanisms of which have not been fully studied to date. Possible mechanisms of heart damage in alcoholism include: the direct toxic effect of ethanol and its metabolite acetaldehyde on the myocardium, the development of electrolyte disorders and thiamine deficiency, the effect of various substances added to alcohol, and the activation of the sympathetic-adrenal system [5]. In addition, the influence of the renin-angiotensin-aldosterone system, cytokines, and natriuretic peptide can also play a significant role [4].

Despite the importance of this problem, there is still no effective treatment regimen for ACM [6,7]. Currently, a set of measures aimed at treating patients with ACM is reduced to stopping alcohol consumption, conducting symptomatic and restorative therapy. At the same time, given that oxidative stress plays a significant role in its pathogenesis, metabolic disorders and transport of free fatty acids, metabolic therapy is pathogenetically substantiated in this disease [8]. In the complex therapy of ACMP, drugs Mildronate [10] and Mexidol [11] have found wide application as metabolitotropic cardioprotectors. However, in real clinical practice, when prescribing these drugs, it is not always possible to achieve an adequate clinical effect [12], which determines the urgent need to search for and create new drugs with a strictly targeted action, taking into account the complex mechanisms of the damaging effect of ethyl alcohol on the myocardium. In this regard, there is undoubted interest in

Puts a combined agent of L-arginine with thiotriazoline in the optimal combination - 4:1, called "Argitril" (development of NPO "Farmatron", Ukraine), which exhibits a cardioprotective effect in experimental myocardial infarction.

The aim of this study was to study the cardioprotective effect of the combined drug L-arginine with thiotriazoline (4:1) in comparison with the classic metabolitotropic drugs Mildronate, Mexidol in terms of the effect on the morpho-functional characteristics of cardiomyocytes under conditions of modeling alcoholic cardiomyopathy.

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Research methods. The experiment was carried out on 50 white outbred male rats weighing 170-180 g, obtained from the nursery of the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine, which were kept in a vivarium with free access to food (standard granulated food) and water, with a natural change of day and night . All experimental procedures were carried out in accordance with the "Regulations on the use of animals in biomedical research", the General principles of work on animals, approved by the 1st National Congress on Bioethics (Kyiv, Ukraine, 2001) and consistent with the provisions of the European Convention for the Protection vertebrates used for experimental and other scientific purposes (Strasbourg, France, 1985).

ACM was induced by intragastric administration of ethanol at a dose of 8 g/kg for 90 days. This model reproduces the structural, functional and metabolic disorders of the myocardium characteristic of ACM [13]. All animals were divided into 5 groups of 10 animals each. The studied drugs were administered intraperitoneally for 30 days - the proposed agent (L-arginine 100 mg/ml + thiotriazoline 25 mg/ml (4:1)) - 200 mg/kg (in terms of L-arginine); Mildronate (Grindeks, Latvia) - 250 mg / kg; Mexidol (OOO NPK Pharmasoft, Russia) – 200 mg/kg [9]. The control and intact groups received saline as an active control. At the end of the studies, the animals were taken out of the experiment 2–4 min after the injection of sodium ethaminal (40 mg/kg) (until the loss of the righting reflex) in order to minimize neurometabolic disorders. For biochemical studies, the heart was washed with chilled 0.15 M KCl (4°C) 1:10, and then crushed in liquid nitrogen to a powder state and homogenized in a 10-fold volume of the medium at (2°C) containing (in mmol): sucrose - 250, Tris-HCl buffer - 20, EDTA - 1 (pH 7.4). At a temperature (+4°C), the cytosolic fraction was isolated by differential centrifugation on a refrigerated centrifuge Sigma 3-30k (Germany) [17]. In the cytosol, the molecular marker of myocardial damage ST2 protein was determined by the solid-phase immunosorbent sandwich ELISA method using the Critical Diagnostics Presage® ST2 Assay kit (REF#BC-1065).

Significance of differences between the experimental groups was carried out using the nonparametric Mann-Whitney U-test. Differences with a significance level of more than 95% ($p<0.05$) were considered significant. The results of the study were processed using the statistical package of the licensed program "STATISTICA for Windows 6.1" (StatSoft Inc., No. AXX R712D833214SAN5), as well as "SPSS 16.0", "Microsoft Excel 2003".

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Research results. As a result of the conducted studies, it was found that on the 30th day after the 90-day alcoholization, ACM is formed in animals. Histologically revealed destructive changes in cardiomyocytes, manifested in the form of fuchsinophilia, anisotropy, accumulation of free lipids in the sarcoplasm. Along with these changes in the myocardium, phenomena of proliferation of connective tissue elements, focal myocardial obesity and the development of severe perivascular cardiosclerosis were found.

A feature of the formation of ACM, unlike other cardiomyopathies, is alcohol-dependent damage to myocardial mitochondria, which makes the mitochondria a source of reactive oxygen species and pro-apoatic proteins, and against the background of deterioration in energy production (a decrease in ATP), activation of oxidative stress and apoptosis is observed [12,13]. A fundamentally important process is the remodeling of the heart. This concept includes: violation of the structure of the contractile apparatus of cardiomyocytes, their functional asymmetry, changes in intercellular interactions, interstitial fibrosis, despiralization of the course of muscle bundles and changes in the shape of the heart cavities. This was confirmed by an increase in the concentration of ST2 protein in the cytosol of the myocardium of control rats (table) by 3.34 times compared with the intact group. ST2 (Suppression of tumorogenicity 2, Growth Stimulation ex-pressed gene 2, stimulating growth factor expressed by gene 2, aka IL1RL1) is a member of the IL-1 receptor superfamily. ST2 is an IL-33 receptor [4]. ST2 is a marker of fibrosis and remodeling of cardiac tissue, released by cardiomyocytes and fibroblasts [4]. An increase in ST2 concentration indicates cardiac remodeling and heart failure in animals with ACM.

The introduction of Mildronate reduced the concentration of ST2 by 17.2% in the myocardium of rats with ACM. The revealed effect of the drug may be due to the fact that Mildronate, indirectly through an increase in the concentration of gamma-butyrobetaine, is able to influence the regulation of NFkB [13].

The introduction of Mexidol reduced the concentration of ST2 by 26.1% in the myocardium of rats with ACM. A number of experimental and clinical studies have established that Mexidol normalizes some mechanisms of energy metabolism in myocardial ischemia, reduces the density of apoptically altered cardiomyocytes [3,13].

Administration of the combined agent L-arginine/thiotriazoline resulted in a 43% decrease in ST2 concentration in the myocardial cytosol of rats with ACM. The strength of the cardioprotective effect of the combination of L-arginine/thiotriazoline significantly exceeds the reference drug Mildronate and Mexidol in conditions with ACM.

Conclusions:

Modeling of alcoholic cardiomyopathy leads to morphological changes in cardiomyocytes in experimental animals - an increase in the concentration of the marker of fibrosis and remodeling of the heart tissue (protein ST2) by 3.34 times compared to the intact group.

2. Course 30-day intraperitoneal administration of metabolitotropic cardioprotectors to animals with ACM in the therapeutic regimen - the combined agent L-arginine/thiotriazoline (200 mg/kg), Mexidol (200 mg/kg) and Mildronate (250 mg/kg) led to changes in different directions and severity of morphological and functional parameters of cardiomyocytes (influence on the level of the ST2 marker in the myocardium of rats with ACM). The combined drug L-arginine with thiotriazoline significantly outperforms the reference drugs Mildronate and Mexidol.

The data obtained are an experimental justification for the use of the combined agent L-arginine/thiotriazoline in the complex therapy of ACM.

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