

Use of Mildronate in Geriatric Patients with Congestive Heart Failure

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Abstract

Aims: The aim of our investigation was to assess effectiveness of Mildronate in the treatment of aged patients with congestive heart failure.

Methods: Ninety one patients with NYHA functioned class I to III heart failure were assessed. Study group consisted of 63 patients who got Mildronate 750 mg per day for one month together with conventional treatment. Control group which consisted of 28 patients got only conventional treatment. Objective and subjective state of study subjects were assessed, questionnaire on quality of life was completed, electrocardiogram was registered and 6 minute walking test was performed.

Results: In the study group angina attacks decreased from 1.6 to 0.7 per day, and its intensity from 1.4 to 0.7 scores (in 7 score system), ($p < 0.05$). In control group angina attacks decreased from 1.46 to 1.25, ($p > 0.05$). Among the study group rales in lungs disappeared in 8 patients (12.6%), and in 3 patients (4.8%) oedema feet subsided. Systolic blood pressure decreased by 8 mmHg and diastolic by 4 mmHg. In control group these clinical changes during the period of study were not statistically significant.

Conclusion: The study showed that mildronate was a safe and well tolerated medication in aged patient and helped to decrease the symptoms of heart failure, increased exercise tolerance and improved quality of life.

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Introduction

What is the solution if some region of the organism lacks oxygen and there is almost no possibility to increase blood flow (like in atherosclerosis and heart failure)?

Coronary heart disease is treated with help of antianginal drugs which reduce heart rate and/or increases coronary blood flow, like nitrates, beta-blockers, calcium channel blockers etc. These drugs improve the hemodynamic indices but they can't optimise oxygen consumption in myocardium. Thus, such remedy alone is not always sufficiently effective. More over, their use is limited by contraindications and side effects.

Search for medicines improving energy metabolism under restricted oxygen supply lasted for a long time. In 1961 trimetazidine was elaborated – the first clinically effective cytoprotective drug. The suggested mechanism of action of this drug was free radical scavenging. Unfortunately, only 35 years later the real mechanism of action of trimetazidine was elucidated. At that moment Latvian scientists had demonstrated that compounds limiting fatty acid oxidation were valuable to diminish oxygen consumption by ischemic myocardium.¹ A new class of cytoprotective agents, namely p-FOX inhibitors (partial fatty acid oxidation inhibitors) were discovered in Riga. This discovery later allowed to introduce in the market Mildronate (MET-88, meldonium), the first medicine with confirmed mechanism of action based on partial fatty acid oxidation inhibition. It was clearly demonstrated that Mildronate acts as a p-FOX inhibitor via gamma-butyrobetaine hydroxylase inhibition, leading to lowering of carnitine concentration both in blood and tissues.

A close similarity of pharmacological effects of both compounds MET-88 and trimetazidine on experimental animals was noted soon. Recently

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published data supported the hypothesis that trimetazidine selectively inhibits long-chain 3-ketoacyl CoA thiolase (LC 3-KAT), thereby reducing fatty acid oxidation inside mitochondrial matrix resulting in clinical benefit. According to its difference in mechanism of action, mildronate belongs to the second generation of p-FOX inhibitors as it inhibits fatty acid transportation across mitochondrial membranes whereas the first generation of p-FOX inhibitors such as trimetazidine and ranolazine acts only inside of mitochondria, blocking only the last step of fatty acid oxidation.^{2,3}

By lowering carnitine levels that Mildronate does not permit fatty acids to penetrate the membranes and the cells are protected from the death in conditions of hypoxia.^{4,5} It has been shown that both approaches, i.e. strong elevation of carnitine over average physiological level in cardiomyocytes or the opposite – the lowering it till 80% of physiological level are contributing positively to the survival of ischemic tissues.⁶ Mildronate initiates switching energy production in myocytes from use of fatty acids to the glucose oxidation and decreases the concentration of fatty acid metabolites in mitochondrial matrix. Therefore ATP transport is improved and survival of cardiomyocytes under ischemic conditions is improved as well.

Mildronate also increases concentration of gamma-butyrobetaine, thus enhancing production of nitric oxide. Nitric oxide is able to neutralize free radicals, decrease resistance of peripheral arteries and vasoconstriction caused by adrenaline, thrombocyte aggregation and increase permeability of erythrocyte membrane. It is shown that Mildronate protects the cells from free radical damage.^{7,8}

Mildronate is effective in optimizing oxygen consumption in patients with coronary heart disease and in healthy subjects. Nevertheless, its effect on geriatric patients was not widely investigated.

The aim of our investigation was to assess effectiveness of mildronate in treatment of aged patients with congestive heart failure.

Material and Methods

Ninety one patients aged 60-80 years having NYHA class I to III heart failure were assessed.⁹ Study group consisted of 63 patients (20 men and 43 women) who got mildronate 750 mg per day for one month together with conventional treatment. The mean age of that group was 65.65 years, body mass index 28.28

kg/m². Control group consisted of 28 patients (6 men and 22 women) who got only conventional treatment. Their mean age was 65.40 years, body mass index 27.41 kg/m².

Inclusion criteria for the study were: patients with age 60 to 80 years old of either sex with class I to II angina pectoris and class I to III heart failure.

Exclusion criteria were:

- acute myocardial infarction, unstable angina, heart valve disease impairing hemodynamics to high grade, uncontrolled arterial hypertension, cardiac arrhythmias severely impairing hemodynamics, atrial flutter, pacemaker implantation;
- refusal to participate in the study, psychiatric diseases, alcohol and drug abuse, participation in other studies;
- significant concomitant diseases (hepatic and renal failure, anaemia, inability to perform physical exercise test, organic diseases of CNS, terminal diseases).

Objective and subjective states of study subjects were assessed including questionnaire on quality of life, electrocardiogram and 6 minute walking test performed.^{10,11}

After the primary investigation, the study group subjects received Mildronate 750 mg per day for four weeks along with conventional treatment while the control group received usual treatment only. After four weeks all examination were repeated.

The data were analyzed using standard statistical methods. Statistical significance was determined by using two tailed *p* values.

Results and Discussion

There was no major difference between study and control group in age, body weight, risk factors, concomitant diseases and consumption of medications. Prevalence of smoking in study group was 1.6% and in control group 3.6%. Diabetes was present in 11.1% and 7.1%, arterial hypertension in 61.9% and 71.4% respectively. In both groups similar percentage of study subjects were treated with antihypertensive drugs, diuretics, calcium channel blockers, antiarrhythmics etc. No patient from either group received digoxin.

The patients tolerated mildronate well. Sixty one patients (96.8%) had no complaints. Two patients

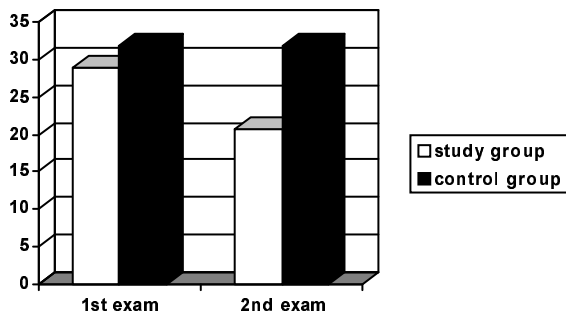


Fig.1. Results of completing quality of life questionnaire.

(3.2%) complained of palpitations and insomnia, requiring discontinuation of Mildronate. Both of these study subjects were using levothyroxine for hypothyroidism.

In trial group attacks of angina, palpitations, headaches and dizziness became less and dyspnoea while performing activities of daily living decreased. Insomnia and anxiety changed insignificantly. In research group prevalence of angina attacks decreased from 1.6 to 0.7 per day, and its intensity from 1.4 to 0.7 scores (in 7 score system), ($p < 0.05$). In control group prevalence of angina attacks decreased from 1.46 to 1.25, ($p > 0.05$).

In trial group in 8 patients (12.6%) rales in lungs disappeared, and in 3 patients (4.8%) oedema of the legs subsided. Systolic blood pressure decreased by 8 mmHg and diastolic by 4 mmHg. In control group these clinical changes during the period of study were statistically not significant.

In research group mean score of quality of life questionnaire decreased from 28.9 to 20.8 points, ($p < 0.05$), implying that quality of life significantly improved (Fig.1). In control group mean score of questionnaire decreased from 31.9 to 31.7 ($p > 0.05$).

Results of six minute walking test are presented in Figure 2. Research group subjects during the first investigation in six minutes walked 381.9 m. After one month of mildronate administration they walked 426.4 m: their walking distance increased significantly. Control group patients during the first visit walked 365.0 m. A month later they walked 359.3 m, ($p > 0.05$). In research group for 5 patients according to results of 6 minute walking test, class of heart failure decreased from the second to the first. In control group in that aspect there was no major change.

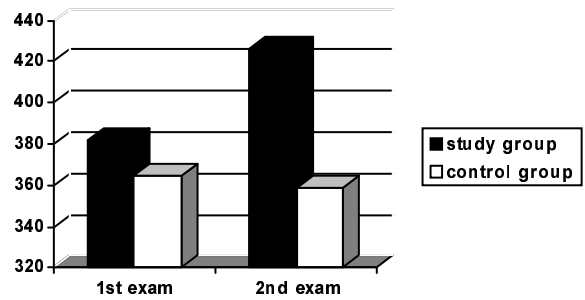


Fig 2. Six minute walking test results during first examination and a month after.

Indications of mildronate use in patients with cardiovascular disease are:

- chronic ischemic heart disease,
- stable angina pectoris,
- functional cardiovascular diseases,
- cardiomyopathies,
- acute and chronic cerebrovascular disease.¹²

In our study, patients got Mildronate because of first three indications. It is noteworthy that no patient used digoxin probably because no patients with atrial fibrillation were included into study. Mildronate decreases the number of ventricular arrhythmias, and does not increase myocardial ischemia during physical exercise.¹³

The fact that mildronate was poorly tolerated by the patients using levothyroxine can be explained by its mechanism of action: mildronate suppresses biosynthesis of carnitine, while carnitine has some antithyroid properties.¹⁴

Clinical investigations performed in middle age patients have shown that mildronate:

- increases functional capacity of myocardium – ejection fraction and cardiac output,
- improves tolerance of physical exercise and quality of life,
- decreases resistance of peripheral arterioles,
- does not cause serious side effects,
- is drug of choice in mild heart failure,
- can be included into the present conventional therapy.¹⁵

According to our results, mildronate was safe and well tolerated in geriatric patients with coronary heart disease presenting with stable angina pectoris and chronic heart failure. It helped to decrease symptoms and signs of heart failure, to increase the tolerance of exercise and at the same time improved quality of life of the patients.

Conclusions

Mildronate is effective in treatment of geriatric patients with congestive heart failure and stable angina pectoris.

It is safe and well tolerated in the elderly patients.

Mildronate improves subjective state of aged patients and their quality of life.

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