A Dose-Dependent Improvement in Exercise Tolerance in Patients With Stable Angina Treated With Mildronate: A Clinical Trial “MILSS I”

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Key words: mildronate; partial fatty acid oxidation inhibition; exercise tolerance; stable angina.

Summary. Objective. To assess the efficacy of various doses of Mildronate in combination with standard therapy for the exercise tolerance of patients with stable angina pectoris. The primary efficacy variable was the change in exercise time in bicycle ergometry from the baseline to 12 weeks of treatment. The secondary endpoints were the changes in maximum achieved load and time to the onset of angina from the baseline to week 12.

Material and Methods. A total of 512 patients with chronic coronary heart disease who had ischemia as the limiting factor in the exercise test from 72 study centers in 4 countries were enrolled in this prospective, randomized, double-blind, placebo controlled phase 2 study. The patients were assigned to either 4 groups receiving standard therapy plus Mildronate at different daily doses or 1 group receiving standard therapy plus placebo.

Results. The mean change in the total exercise time in the mildronate 100 mg and mildronate 300 mg groups was −2.12±108.45 and 11.48±62.03 seconds, respectively. The mean change for the placebo group was −7.10±81.78 seconds. The difference between Mildronate 100 mg and 300 mg and placebo groups was not significant. Patients in the Mildronate 1000 mg group showed a remarkable increase in the mean change in the total exercise time (35.18±53.29 seconds, P=0.002). Mildronate at a dose of 3000 mg caused a smaller increase as compared with a dose of 1000 mg. Similar changes in the secondary end parameters were observed.

Conclusion. The most effective dose of Mildronate in combination with standard therapy was found to be 500 mg twice a day.

Introduction

A possible alternative of medical treatment of ischemic conditions is the use of pharmaceutical products having so-called “metabolic” activity, i.e., products acting mainly on selected mechanisms of tissue energetic metabolism. Mildronate, a partial inhibitor of fatty acid oxidation (p-FOX), is the representative of this group of pharmaceutical products.

Mildronate is a structural aza-analogue of the carnitine precursor gamma-butyrobetaine (GBB). It inhibits carnitine biosynthesis reversibly competing for gamma-butyrobetaine hydroxylase. It has been shown that mildronate inhibits carnitine reabsorption in the kidneys of rats by renal brush-border membrane (1). Thus, carnitine is not reabsorbed into the circulatory system to re-enter metabolic pathways, but is directly eliminated from the organism. This results in reduced tissue (2) and plasma (3) concentrations of carnitine. Thereby, long-chain fatty acid transport through internal mitochondrial membranes is inhibited. That, in turn, further enhances the transport of entire ATP produced in cytosol and delayed β-oxidation of fatty acids, and prevents the accumulation of unoxidized fatty acids – acyl-carnitine and acyl-coenzyme A – in mitochondria. An increased cytosol concentration of fatty acids is a specific signal to cells that the fatty acid oxidation is not possible. The body responds to such a signal by the initiation of the glucose oxidation mechanisms (4). Reduced concentration of carnitine in the body stimulates the synthesis of its precursor GBB (5), which activates NO synthetase thus causing both vasodilatation and antivasospasmic effects. The capability of GBB to dilate spastic blood vessels selectively is important, since this ensures blood supply to ischemic areas without provoking a steal effect for the healthy parts of myocardium (6, 7).

The efficacy of mildronate for the treatment of myocardial ischemia has been proved in experiments and clinics by improved systolic function of myocardium, inhibited hypertrophy and dilatation of myocardium, improved peripheral blood circulation (increased contractility of arteriole smooth muscles), increased stress tolerance, reduced anginal symptoms, and improved quality of life (8–13).

Mildronate has been approved for clinical use

*Principal investigators from 72 study centers are listed at the end of the article.
in patients with stable angina in Latvia, Lithuania, Russia, Ukraine, and Georgia. The usual dose in clinical practice is 500 mg twice daily, but there are no dose-response data from adequate placebo-controlled trials.

The aim of this study was to assess the efficacy and safety of mildronate at various doses in combination with standard therapy for the exercise tolerance of patients with stable angina pectoris.

**Material and Methods**

The study was conducted in accordance with the principles set forth in the Good Clinical Practice (GCP), the International Conference of Harmonisation (ICH) (CPMP/ICH/135/95), the Helsinki Declaration (1964, amended in 2002), the Guidance on the Clinical Investigation of Anti-Anginal Medicinal Products in Stable Angina Pectoris (CPMP/EWP/234/95/rev. 1), and any applicable national regulatory requirements.

The study was a prospective, randomized, double-blind, placebo-controlled phase 2 study with 5 treatment groups.

**Study Population.** The study included 512 male and female patients with chronic coronary heart disease (CHD, functional class II–III) according to the Canadian Cardiovascular Society (CCS) who had ischemia as the limiting factor in the exercise test. If found eligible, the patients were randomized (double-blindly) at visit 4 following the run-in period to receive either placebo or Mildronate at one of the 4 doses (2×50 mg/day, 2×150 mg/day, 2×500 mg/day, and 2×1500 mg/day). Randomization was stratified by study sites. The study was performed in 74 sites of 4 countries (Russian Federation, Ukraine, Georgia, and Latvia).

The distribution of patients is shown in Table 1. All treatment groups were comparable with respect to their demographic characteristics. There were more males than females (75.4% in the mildronate 100 mg group, 70.8% in the mildronate 300 mg group, 72.6% in the mildronate 1000 mg group, 71.2% in the mildronate 3000 mg group, and 72.1% in the placebo group). One woman in the mildronate 100 mg group, 1 woman in the mildronate 300 mg group, and 2 women in the placebo group had premenopausal status.

The mean age of the patients at the date when written informed consent was signed was 61.36 years in the mildronate 100 mg group, 60.80 years in the mildronate 300 mg group, 61.20 years in the mildronate 1000 mg group, 61.26 years in the mildronate 3000 mg group, and 59.78 years in the placebo group.

Most of patients were nonsmokers, i.e., 414 patients (73.7% of patients in the mildronate 100 mg group, 80.2% in the mildronate 300 mg, 87.7% in the mildronate 1000 mg, 85.6% in the mildronate 3000 mg, and 79.8% in the placebo group). From current nonsmokers, 32.6% in the mildronate 100 mg group, 36.5% in the mildronate 300 mg group, 28.6% in the mildronate 1000 mg group, 25.3% in the mildronate 3000 mg group, and 36.1% in the placebo group were former smokers. The mean duration of smoking among current smokers was 31 years in the mildronate 100 mg group, 33 years in the mildronate 300 mg group, 37 years in the mildronate 1000 mg group, 31 years in the mildronate 3000 mg group, and 29 years in the placebo group.

**Medical History and Concomitant Diseases.** The most common concomitant diseases were vascular disorders (87 cases in the mildronate 100 mg group, 85 cases in the mildronate 300 mg group, 55 cases in the mildronate 1000 mg group, 84 cases in the mildronate 3000 mg group, and 74 cases in the placebo group), health conditions requiring surgical and medical procedures (39 cases in the mildronate 100 mg group, 42 cases in the mildronate 300 mg group, 14 cases in the mildronate 1000 mg group, 17 cases in the mildronate 3000 mg group, and 37 cases in the placebo group), gastrointestinal disorders (37 cases in the mildronate 100 mg group, 34 cases in the mildronate 300 mg group, 25 cases in the mildronate 1000 mg group, 31 cases in the mil-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mildronate 100 mg (N=118)</th>
<th>Mildronate 300 mg (N=106)</th>
<th>Mildronate 1000 mg (N=73)</th>
<th>Mildronate 3000 mg (N=111)</th>
<th>Placebo (N=104)</th>
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<td>20</td>
<td>32</td>
<td>27</td>
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<tr>
<td>Age, mean (SD) [range], years</td>
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<td>60.80 (8.60)</td>
<td>61.20 (8.67)</td>
<td>61.26 (8.81)</td>
<td>59.78 (8.66)</td>
</tr>
<tr>
<td></td>
<td>[37.10–82.82]</td>
<td>[35.96–77.65]</td>
<td>[40.02–79.51]</td>
<td>[39.99–81.31]</td>
<td>[41.62–79.58]</td>
</tr>
</tbody>
</table>

**Table 1. Demographic Characteristics of the Patients**

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dronate 3000 mg group, and 22 cases in the placebo group), metabolism and nutrition disorders (28 cases in the mildronate 100 mg group, 28 cases in the mildronate 300 mg group, 25 cases in the mildronate 1000 mg group, 29 cases in the mildronate 3000 mg group, and 36 cases in the placebo group), and cardiac disorders (other than coronary artery disease [CAD]) (24 cases in the mildronate 100 mg group, 26 cases in the mildronate 300 mg group, 23 cases in the mildronate 1000 mg group, 17 cases in the mildronate 3000 mg group, 27 cases in the mildronate 100 mg group, 28 cases in the mildronate 300 mg group, and 19 cases in the placebo group).

The treatment groups were comparable regarding medical history and the frequency of concomitant diseases.

History of Coronary Artery Disease Before study. The degree of CAD diagnosed by angiography was as follows: single-vessel CAD was diagnosed for 4 patients (3.4%) in the mildronate 100 mg group, 10 patients (9.4%) in the mildronate 300 mg group, 2 patients (2.7%) in the mildronate 1000 mg group, 5 patients (4.5%) in the mildronate 3000 mg group, and 5 patients (4.8%) patients in the placebo group; two-vessel CAD, for 10 patients (8.5%) in the mildronate 100 mg group, 5 patients (4.7%) in the mildronate 300 mg group, 10 patients (13.7%) in the mildronate 1000 mg group, 8 patients (7.2%) in the mildronate 3000 mg group, and 2 patients (1.9%) in the placebo group; three-vessel CAD, for 14 patients (11.9%) in the mildronate 100 mg group, 9 patients (8.5%) in the mildronate 300 mg group, 8 patients (11.0%) in the mildronate 1000 mg group, 11 patients (9.9%) in the mildronate 3000 mg group, and 16 patients (15.4%) in the placebo group. Ninety patients (76.3%) in the mildronate 100 mg group, 82 patients (77.3%) in the mildronate 300 mg group, 53 patients (72.6%) in the mildronate 1000 mg group, 87 patients (78.4%) in the mildronate 3000 mg group, and 81 patients (77.9%) in the placebo group did not undergo angiography to identify the degree of CAD.

Standard and Additional Therapies for Angina. The use of standard therapy for angina in all the treatment groups is shown in Table 2.

Concerning the additional therapy of angina, 76.1% of patients in the mildronate 100 mg group, 71.2% of patients in the mildronate 300 mg group, 76.3% of patients in the mildronate 1000 mg group, 67.8% of patients in the mildronate 3000 mg group, and 80.0% of patients in the placebo group used long-acting nitrates. Half (50.0%) of patients in the mildronate 100 mg group, 48.1% patients in the mildronate 300 mg group, 34.2% patients in the mildronate 1000 mg group, 47.5% patients in the mildronate 3000 mg group, and 35.4% patients in the placebo group used calcium channel blockers as the additional therapy for angina in the study population.

Weighing up the benefits and risks, placebo treatment for 12 weeks appeared to be acceptable, since the patients were receiving individually adjusted standard treatment for CHD during the whole period of the study. The follow-up time was planned for 17 weeks: 4 weeks run-in period + 12-week randomized therapy + 1-week poststudy follow-up.

The study medication was applied orally twice a day. The patients visited the study centers regularly in order for the investigator to evaluate efficacy, safety, and tolerability as outlined in the study flowchart.

In order to investigate the study objective and document the findings, a bicycle ergometry was used, which is a standard examination method for patients with CHD.

The primary efficacy variable for this study was the change in exercise time during bicycle ergometry from the baseline to 12 week after treatment with mildronate or placebo.

The baseline was defined as the mean exercise time of the last two measurements of the run-in period. The secondary endpoints were the changes in the maximum achieved load (W) and time to the onset of angina from the baseline to week 12.

Exercise test was performed on a standard bicycle ergometer at least 12 hours after the intake of mildronate or placebo and standard antianginal therapy (except short-acting nitrates). The initial load was 50 W, which was increased by 25 W at 3-minute intervals. Indications for stopping the exercise test were as follows: severe exhaustion, severe dyspnea, anginal attack, dizziness, ST-depression more than 1 mm, persistent drop in systolic blood pressure (below 90 mm Hg), serious ventricular arrhythmias, supraventricular tachycardia, or atrio-

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mildronate 100 mg (N=118)</th>
<th>Mildronate 300 mg (N=106)</th>
<th>Mildronate 1000 mg (N=73)</th>
<th>Mildronate 3000 mg (N=111)</th>
<th>Placebo (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blocker</td>
<td>111 (94.1)</td>
<td>102 (96.2)</td>
<td>69 (94.5)</td>
<td>107 (96.4)</td>
<td>103 (99.0)</td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td>115 (97.5)</td>
<td>100 (94.3)</td>
<td>69 (94.5)</td>
<td>107 (96.4)</td>
<td>101 (97.1)</td>
</tr>
<tr>
<td>Statin</td>
<td>89 (75.4)</td>
<td>79 (74.5)</td>
<td>57 (78.1)</td>
<td>76 (68.5)</td>
<td>83 (80.6)</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor antagonist</td>
<td>91 (77.1)</td>
<td>83 (78.3)</td>
<td>61 (83.6)</td>
<td>92 (83.6)</td>
<td>81 (78.6)</td>
</tr>
</tbody>
</table>

Values are number (percentage). ACE, angiotensin-converting enzyme.
ventricular block.

During and before the termination of the test, heart rate, blood pressure, and magnitude of changes in ST segment (at the end of each workload and on the termination of the test) were recorded. The total exercise time and the highest achieved workload were recorded. ST-segment depression was measured 80 ms from J-point.

Statistical Analysis. The comparability of the 5 treatment groups was checked by computing descriptive statistics for all the baseline characteristics. Additionally, formal statistical methods were used to flag potential differences between the treatment groups. For this purpose, the Kruskal-Wallis test was used for continuous variables, and the Cochran-Mantel-Haenszel was employed for categorical variables.

Analysis of covariance (ANCOVA) model was used to evaluate the overall difference between the treatments and pairwise comparisons. The model included the treatment group and the center/country as fixed factors. The baseline measurement was used as a covariate in the model. The overall difference and pairwise comparisons described above (4 doses of mildronate compared with placebo) were estimated using contrasts. Estimates of the treatment differences and two-sided 95% confidence intervals were reported in addition to \( P \) values.

The comparisons for the secondary variables were similar to the primary variable. First, the overall difference among all 5 doses (4 doses of mildronate and placebo) was evaluated. If there was an overall difference, the pairwise comparisons between each of the 4 doses of mildronate and placebo were done. No adjustment for the multiplicity (i.e., the hierarchical closed test procedure) was done for the secondary variables.

Results

Primary Endpoint. The hypothesis being behind the study was that there was a dose-related improvement in exercise capacity in CHD patients treated with mildronate. The hypothesis of superiority in the change in the exercise time in VEM (bicycle ergometry) was tested. The hypothesis was tested by the nonparametric Mann-Whitney test.

The mean change in the total exercise time in the mildronate 100 mg group was \(-2.12\pm108.45\) seconds, while the placebo group showed a mean value of \(-7.10\pm81.78\) seconds; however, the difference was not significant (\( P=0.478 \)) (Fig.). The mildronate 300 mg group showed an improvement in the mean change in the total exercise time from the baseline to week 12 (11.48\pm62.03 seconds). However, this improvement was not significant with respect to the placebo group (\( P=0.249 \)). The patients from the mildronate 1000 mg group had a remarkable increase in the mean change in the total exercise time from the baseline to week 12 (35.18\pm53.29 seconds), and this difference was significant as compared with the placebo group (\( P=0.002 \)). The mildronate 3000 mg group showed a mean 28.08\pm88.94-second change in the total exercise time that was smaller than in the mildronate 1000 mg group, but still significant with respect to the placebo group.

The same relationship in dynamics of total exercise time was observed in different age groups (Table 3).

In the study population aged 70 years and less, the mean change in the total exercise time from the baseline to week 12 was 1.38\pm108.29 seconds in the mildronate 100 mg group, 15.75\pm63.61 seconds in the mildronate 300 mg group, 36.83\pm55.70 seconds in the mildronate 1000 mg group, 34.78\pm91.95 seconds in the mildronate 3000 mg group, and –4.72\pm82.08 seconds in the placebo group. The difference between the mildronate 100 mg and placebo groups was insignificant (\( P=0.160 \)), and that between the mildronate 300 mg and placebo groups was significant (\( P=0.031 \)). The mildronate 1000 mg and 3000 mg groups showed a highly significant improvement comparing with the placebo group (\( P=0.002 \) and \( P=0.003 \), respectively).

For patients older than 70 years, the mean change in the total exercise time from the baseline to week 12 was –20.00\pm110.59 seconds in the mildronate 100 mg group, –3.07\pm55.21 seconds in the mildronate 300 mg group, 22.15\pm35.65 seconds in the mildronate 1000 mg group, –6.66\pm62.69 seconds in the mildronate 3000 mg group, and –23.38\pm81.20 seconds in the placebo group. The following differences between treatment groups were judged as insignificant: between the mildronate 100 mg and placebo groups (\( P=0.316 \)), the mildronate 300 mg and placebo groups (\( P=0.273 \)), and the mildronate 3000 mg and placebo groups (\( P=0.193 \)). The differ-
ence between the mildronate 1000 mg and placebo groups was significant ($P=0.013$).

The results by the reason of stopping the exercise test are shown in Table 4. In case if several reasons were indicated, the main was used.

The most common reason of stopping the exercise test was anginal attack in all the treatment groups. For these patients, the mean change in the total exercise time from the baseline to week 12 was $-5.45\pm111.13$ seconds in the mildronate 100 mg group, $23.32\pm62.84$ seconds in the mildronate 300 mg group, $35.69\pm55.90$ seconds in the mildronate 1000 mg group, $33.51\pm91.67$ seconds in the mildronate 3000 mg group, and $-4.56\pm77.65$ seconds in the placebo group.

For the patients having severe exhaustion as the reason of stopping the exercise test, the higher mean change in the total exercise time from the baseline to week 12 was in the mildronate 1000 mg group ($27.63\pm42.16$ seconds). The same relationship was observed for the patients having ST-segment depression more than 1 mm as the reason of stopping the exercise test and for patients with other reasons of stopping the exercise test.

The results by CCS functional class at the randomization visit are shown in Table 5.
For the patients with CCS functional class 2 and 3 at the randomization visit, the highest mean change in the total exercise time from the baseline to week 12 was in the mildronate 1000 mg group (45.63±57.59 and 14.73±36.74 seconds, respectively).

Secondary Efficacy Variables. Maximum Achieved Load. The descriptive statistics for the change in maximum achieved load (MAL) in W from the baseline to week 12 are shown in Table 6.

The mean change in the maximum achieved load was –0.11±17.80 W in the mildronate 100 mg group, 2.19±11.12 W in the mildronate 300 mg group, 5.63±11.34 W in the mildronate 1000 mg group, 3.34±16.12 W in the mildronate 3000 mg group, and 0.37±14.04 W in the placebo group. The differences between the mildronate 100 mg, 300 mg, and 3000 mg and placebo groups were insignificant (P =0.581, P =0.702, and P =0.437, respectively). The only significant difference was between the mildronate 1000 mg and placebo groups (P =0.026).

Time to Onset of Angina. The descriptive statistics for time to the onset of angina are given in Table 7.

At the baseline, the mean time to onset of angina in the mildronate 100 mg group was 387.96±130.87 seconds, in the mildronate 300 mg group 376.39±119.85 seconds, in the mildronate 1000 mg group 376.39±119.85 seconds, in the mildronate 3000 mg group 376.39±119.85 seconds, in the placebo group 376.39±119.85 seconds.

Table 5. Descriptive Statistics for the Change in the Total Exercise Time in Seconds From Baseline to Week 12 by CCS Functional Class at the Randomization Visit

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Mildronate 100 mg</th>
<th>Mildronate 300 mg</th>
<th>Mildronate 1000 mg</th>
<th>Mildronate 3000 mg</th>
<th>Placebo</th>
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<td>Class 2</td>
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<td></td>
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<td>No. of patients</td>
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<tr>
<td>Minimum</td>
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<td>–122.50</td>
<td>–30.00</td>
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<td>Maximum</td>
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<td>155.50</td>
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<tr>
<td>Mean</td>
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<td>SD</td>
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<td>Mean</td>
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<td>SD</td>
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*P =0.026.

Table 6. Descriptive Statistics for the Change in the Maximum Achieved Load in W From Baseline to Week 12

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Mildronate 100 mg</th>
<th>Mildronate 300 mg</th>
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<td>–12.50</td>
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<tr>
<td>Mean</td>
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<td>SD</td>
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<td>11.12</td>
<td>11.34</td>
<td>16.12</td>
<td>14.04</td>
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Table 7. Descriptive Statistics for Time to the Onset of Angina in Seconds by Treatment Groups
362.15±119.92 seconds, in the mildronate 3000 mg group 373.42±119.12 seconds, and in the placebo group 379.08±125.14 seconds. No significant differences in the mean time to onset of angina comparing the groups were found.

At week 12, the highest increase in time to onset of angina was observed in the mildronate 1000 mg group: from 362.15±119.92 seconds at the baseline to 382.49±142.29 seconds at week 12. An increase was also observed in the mildronate 3000 mg group: from 373.42±119.12 seconds at the baseline to 383.52±171.13 seconds at week 12. In other groups, a decrease in the mean time to onset of angina was documented: from 387.9±130.87 seconds at the baseline to 386.10±154.92 seconds at week 12 in the mildronate 100 mg group, from 376.39±119.85 seconds to 370.52±161.50 seconds at week 12, respectively, in the mildronate 300 mg group, and from 379.08±125.14 seconds to 359.57±151.61 seconds, respectively, in the placebo group.

The differences in the time to onset of angina comparing the mildronate 100 mg, mildronate 300 mg, mildronate 1000 mg, and mildronate 3000 mg with the placebo groups at week 12 were not significant.

**Discussion**

This is the first report of the dose-dependent effects of mildronate on exercise tolerance in coronary heart disease patients with stable angina.

To date, the efficacy of mildronate for the treatment of myocardial ischemia has been proved in clinical practice by the improved systolic function of myocardium, inhibited hypertrophy and dilatation of myocardium, improved peripheral blood circulation (increased contractility of arteriole smooth muscles), increased stress tolerance, reduced anginal symptoms, and improved quality of life (9–13). All cited authors used mildronate at a daily dose of 1000 mg (500 mg twice a day). This dose is used on empirical basis, which does not correspond to the criteria of evidence-based medicine.

Therefore, this study is the first attempt to identify the most effective dose of mildronate using the relatively long (12 weeks) prospective, randomized, double-blind, placebo-controlled trial. For the primary efficacy evaluation, the hypothesis of dose-related improvement of the change in the total exercise time in VEM (bicycle ergometry) from the baseline to week 12 was tested at the 95% level of significance.

It is important to note that at the baseline, the patients of treatment groups were comparable with respect to demographic data, disease anamnesis, medical history data, use of concomitant medications, and smoking habits.

Our results show an increase in the primary efficacy variable (the change in exercise time in bicycle ergometry from the baseline to 12 weeks) in the mildronate 300 mg, 1000 mg, and 3000 mg treatment groups with the highest increase in the mildronate 1000 mg group, whereas a slight decrease in this parameter in the mildronate 100 mg and placebo groups was documented. Therefore, the greatest improvement in the total exercise time comparing the baseline and week 12 was achieved in the mildronate 1000 mg group. The difference between the mildronate 1000 mg and placebo groups was highly significant (P=0.002).

The analysis of primary efficacy variable in two age subgroups and groups by reason of stopping the exercise test showed the same dynamics.

The highest mean change in maximum achieved load was documented in the mildronate 1000 mg group; the difference between the mildronate 1000 mg group and placebo group was significant (P=0.026). The differences between the mildronate 100 mg, 300 mg, and 3000 mg and placebo groups were not significant.

The highest increase in time to onset of angina was observed in the mildronate 1000 mg group: from 362.15±119.92 seconds at the baseline to 382.49±142.29 seconds at week 12. In addition, an increase was observed in the mildronate 3000 mg group.

The study provides evidence that Mildronate at doses of 1000 mg 3000 mg can be used to achieve a positive clinical response. In case of making decision in favor of the higher dosage, the relationship between the dosage and feasible side effects should be taken into account. This means that an increase in dosage can work against the desired effect and evoke side effects (14). No safety profile with regard to different dosages was analyzed in this study, but the data obtained in previous studies have confirmed the safety of mildronate at a dose of 1000 mg as long-term additional therapy (12). The mentioned facts support theoretical and practical speculations that a 3-fold higher dose of mildronate (3000 mg) is more likely to provoke side effects. Thus, the administration of 3000 mg is not a rational decision in clinical practice.

**Conclusions**

This study shows that treatment with mildronate in combination with standard therapy for the exercise tolerance of patients with stable angina pectoris is superior to treatment with placebo in combination with standard therapy. The effect of mildronate on the improvement of exercise tolerance in patients with stable angina was found to be dose-dependent. The most effective and recommended dose of mildronate in combination with standard therapy was found to be 500 mg twice a day.

**Statement of Conflict of Interest**

The authors state no conflict of interest.
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