Original paper

Partial inhibition of fatty acid oxydation increases the exercise tolerance of patients with peripheral arterial disease: the Mildronate Study

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Summary

The objective of the study was to assess the efficacy and safety of the treatment with mildronate (1 g/day) in combination with standard therapy for the exercise tolerance of patients with peripheral arterial disease (PAD).

Design and Methods: The study was a prospective, randomized, double-blind, placebo controlled phase II study with two treatment groups. The study totally included 62 male and female patients with PAD and intermittent claudication as a limiting factor for physical load (the treadmill test). The follow-up time comprised 33 weeks: a 5-week run-in period plus 24 weeks of randomized therapy followed by a 4-week follow-up period.

Results: The mean value of the change in the absolute claudication distance (ACD) during the treadmill test in the mildronate group after 24 weeks of treatment was 231.22 ± 179.02 meters, while the placebo group patients had the mean value of 126.67 ± 120.72 meters. The difference between the treatment groups was significant (p-value = 0.026).

The mean value of the change in the initial claudication distance (ICD) before and after 24 weeks of double-blind therapy during the treadmill test in the mildronate group was 123.93 ±114.73 meters, while the placebo group patients had the mean value of 50.30 ±62.56 meters. The difference between the treatment groups was significant (p-value = 0.033).

The mean value of the change in the ACD from visit T24 (24 weeks of treatment) till one month after the discontinuation of the treatment (visit PT) during the treadmill test in the mildronate group was 19.68 ± 85.58 meters, while the placebo group patients had the mean value – 31.43 ±79.17 meters. The difference between the treatment groups was significant (p-value = 0.032).

Conclusions: The study confirms the superiority of treatment with mildronate (1 g/day) versus placebo in combination with standard therapy for the improvement of exercise tolerance in patients with PAD. The 4 weeks interruption of the mildronate course without loosing the effect could be acceptable in cases of the long-term use of mildronate.

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Introduction

The main principles of pharmacotherapy of tissue ischemic conditions (i.e. myocardium, skeletal muscles, brain, etc.) are the following: 1) the reduction of risk factors (dyslipidemia, diabetes, hypertension, smoking, etc.); 2) the use of antiagregants; 3) the use of vasoactive drugs. A possible alternative of medical treatment is the use of pharmaceutical products having so-called "metabolic" activity, i.e. products acting mainly on selected mechanisms of tissue energetic metabolism. Partial inhibitors of fatty acid oxidation (p-FOX) are the representatives of this group of pharmaceutical products.

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This new class of drugs includes trimetazidine (Preductal, Servier), ranolazine (Ranexa, CVT) and mildronate (Grindeks) that all are in clinical use in some countries.

The effect of mildronate on the cardiovascular system, based on its anti-ishemic and cytoprotective effect has been investigated under experimental and clinical conditions (coronary heart disease, congestive heart failure, cerebral disorders and their experimental models), especially during the last 10 years [1–16].

The results of experimental studies and clinical experience suggest that adding an effective dose of mildronate to conventional antianginal therapy could significantly reduce the symptoms of angina, increase exercise tolerance and improve the quality of life.

As mentioned above, the cytoprotective effect of mildronate allows to assume its clinical effect also in peripheral arterial disease (PAD), particularly in atherosclerosis obliterans of the leg arteries, i.e. under conditions of muscle ischemia. This is of high importance due to the fact that results of treatment of intermittent claudication with medications of other drug groups (vasodilators, pentoxyphylline, statins, propionyl-L-carnitine) are inconvincible [17–23].

This disease is one of the classic situations of tissue ischemia when mildronate as a p-FOX agent could be used for switching energetic metabolism from fatty acid oxidation to glucose oxidation, which demands less oxygen. Unfortunately, only few studies are available up to now.

The study conducted by Gorbunov et al. showed an increase in exercise tolerance within 2.5 months in patients receiving mildronate in daily dose 1.0 g. Patients having a lower stage of claudication had a better response [24]. The importance of this study was not high, as the number of involved patients was low (20 persons) and there was no control group.

So, up to now, the mildronate clinical investigations of PAD has been performed on casual basis, thus do not meet the principles of evidence based medicine. The question regarding the mildronate's clinical effect on PAD is still unresolved.

The objective of the study was to assess the efficacy and safety of the treatment with mildronate (1 g/day) in combination with standard therapy for the exercise tolerance of patients with PAD.

The aim of the study was to assess the efficacy of mildronate using the indices of exercise capacity for patients with PAD. The study was designed to investigate whether statistically significant improvement in the ACD (maximal walking) of the treadmill test could be achieved by mildronate thus indicating its anti-ischemic properties compared to placebo in patients with PAD.

Design and Methods

The study was a prospective, randomized, double-blind, placebo controlled phase II study with two treatment groups: patients in the first group received mildronate + standard therapy, whereas patients in the second group received placebo + standard therapy. The study totally included 62 male and female patients with PAD and intermittent claudication as a limiting factor for physical load, according to the Fontaine classification of PAD in I and II stages.

The primary endpoint of the study was the change in the absolute intermittent claudication (*claudicatio intermittens*) distance (ACD) comparing the ACD before and after 24 weeks of double-blind therapy (visits R and T24).

Secondary endpoints were:

1. Changes in the ACD, comparing other visits than those as in the primary endpoint.
2. Changes in the initial intermittent claudication (*claudicatio intermittens*) distance (ICD) (pain-free walking distance) comparing all visits with visit R.

If found eligible, patients were randomized in 1:1 ratio to receive either mildronate or placebo at visit R, following the run-in period (30 patients in the mildronate group and 32 patients in the placebo group. Screened for randomization and treated at least once (safety population): 62 patients; patients completed all visits (study population): 57 patients. The distribution of patients according to sex in the treatment groups is shown in Table 1.

Table 1.
Demographic characteristics

Variable		Safety population		Study population	
		Mildronate ($N = 30$)	Placebo ($N = 32$)	Mildronate ($N = 27$)	Placebo ($N = 30$)
Sex					
Male	*N*	28	25	26	24
Female	*N*	2	7	1	6

Table 2.
Study flowchart

Procedures	Visit A-5 5 weeks before randomization	Visit A-1 1week before randomization	Rando-misation visit R	Treatment period T4 4 weeks after R	Treatment period T12 12 weeks after R	Treatment period T24 24 weeks after R	Post Treatment PT 4 weeks after treatment
Informed Consent	X						
Clinical Examination	X	X	X	X	X	X	X
Chest X-ray	X						X
ECG at rest	X		X	X	X	X	X
Treadmill test	X	X	X	X	X	X	
Ankle-brachial index	X		X		X	X	X
Inclusion/Exclusion Criteria	X	X	X				
Compliance with randomization criteria			X				
Clinical Laboratory Assignment (haematology, urine-analysis, biochemistry)	X		X	X	X	X	X
Pregnancy Test (if applicable)		X	X	X	X	X	X
Standard Therapy Monitoring	X	X	X	X	X	X	X
Concomitant Therapy Monitoring	X	X	X	X	X	X	X
Smoking Habits Control	X	X	X	X	X	X	X
Control of Dispense Investigational Product			X	X	X	X	
Adverse event monitoring		X	X	X	X	X	X

Both treatment groups were comparable with respect to their demographic characteristics. There were more males (96.3% in the mildronate group and 80.0% in the placebo group) than females (3.7% in the mildronate group and 20.0% in the placebo group). The mean age of the study population was 63.27 years in the mildronate group and 61.03 years in the placebo group. The mean body weight in the mildronate group was 73.2 ± 10.0 kg and in the placebo group it was 77.3 ± 15.1 kg. The mean body mass index was 24.4 ± 3.2 kg/m^2 in the mildronate group and 25.6 ± 3.9 kg/m^2 in the placebo group. Most of the patients were smokers, i.e. 40 patients (20 patients in the mildronate group and 20 patients in the placebo group) of the study population.

The mean duration of intermittent claudication was 2.98 ± 2.43 years in the mildronate group and 3.02 ± 2.09 years in the placebo group. Surgical revascularization was performed in 11 patients in the mildronate group and in 10 patients in the placebo group. The treatment groups were comparable regarding the frequency of medical history and concomitant diseases. Most concomitant diseases were vascular disorders (49 cases in the mildronate group and 51 in the placebo group).

The follow-up time was planned for 33 weeks: a 5-week run-in period plus 24 weeks of randomized therapy followed by a 4-week follow-up period without mildronate therapy.

Weighing up the benefits and risks, placebo treatment for 24 weeks appeared to be acceptable, since the patients were receiving the individually adjusted standard of care treatment for PAD during the whole duration of the study. The study medication (500 mg mildronate or placebo) had to be applied orally twice a day. The patients visited the study centre regularly: in the 4th, 12th and 24th week after the randomization visit and the 4th week after the cessation of mildronate therapy in order to evaluate the efficacy, safety and tolerability of mildronate, as outlined in the study flowchart (Table 2).

The patients underwent the study procedures and follow-up in P. Stradins Clinical University Hospital and the Research Institute of Cardiology, University of Latvia.

An exercise test had to be performed on a standard treadmill equipment (Hewlett-Packard Cosmos Mercury med 4.0) 4 to 6 hours after the

intake of the previous dose of the double blind study drug. During the test a constant speed of the treadmill – 3.2 km/h was used together with a variable tilt, which was increased by 2% every 2 minutes.

The patients had to continue walking on the treadmill until the subjective maximal threshold, which was set as the ACD. Additionally, the ICD, i.e. the distance covered until the appearance of pain in legs was also recorded. During the exercise test, as well as 3 and 5 minutes after its completion, the ECG was recorded and blood pressure measured.

Besides the pain in legs, the following was accepted as a trigger for stopping the exercise test: marked shortness of breath, angina pectoris attack, exhaustion, depression of ST segment more than 1 mm, significant heart rhythm disorders, and instant drop of systolic blood pressure.

Statistical methods The primary efficacy analysis was performed on the study population. The hypothesis of superiority in the comparing ACD during the treadmill exercise test before (randomization) and after 24 weeks of double-blind therapy (visits R and T24) was tested:

H_0: mildronate is not superior to placebo with respect to the treatment of intermittent claudication in patients with PAD.
H_1: mildronate is superior to placebo with respect to the treatment of intermittent claudication in patients with PAD.

The hypothesis was tested by the non-parametric Mann-Whitney test.

All analyses of secondary efficacy variables were based on the study population. Two analyses were conducted: the study population analysis for the observed cases using data from all available visits and using the "last observation carried forward" approach at the final visit. The secondary variables were analyzed using the same models as with the primary efficacy variable. Descriptive statistics were used, in terms of treatment differences in the study population.

Results

Primary endpoint

The statistics of ACD changes during the treatment period in both treatment groups is summarized in Table 3.

The mean value of the change in the ACD during the treadmill test in the mildronate group was 231.22 ± 179.02 meters, while the placebo group patients had the mean value of 126.67 ± 120.72 meters. The difference between the treatment groups was significant (p-value = 0.026).

The dynamics of ACD during the whole study period is summarized in Table 4.

The data summarized in Table 5 revealed the positive dynamics of the ACD from visit to visit in both groups starting from visit R although the remarkable difference occurred between the mildronate and Placebo treatment groups, especially in Visit PT.

The calculated data of dynamics of ACD are depicted in Figure 1.

Secondary endpoints

The changes in the absolute claudication distance

The mean value of the change in the ACD before and after 4 weeks of double-blind therapy during the treadmill test in the mildronate group was 85.04 ± 93.44 meters, while the placebo group patients had the mean value of 54.67 ± 82.31 meters. The difference between the treatment groups was non-significant (p-value = 0.141).

The mean value of the change in the ACD before and after 12 weeks of double-blind therapy in the mildronate group was 176.07 ± 154.85 meters, and in the placebo group – 67.67 ± 89.69 meters. The difference between the treatment groups was highly significant (p-value = 0.003).

The mean value of the change in the ACD from visit T24 to one month after the discontinuation of the treatment (visit PT) during the treadmill test in the mildronate group was 19.68 ± 85.58 meters, while the placebo group patients had the mean value of –31.43 ± 79.17 meters. The difference between the treatment groups was significant (p-value = 0.032).

The changes in the initial claudication distance

The mean value of the change in the ICD before and after 12 weeks of double-blind therapy during the treadmill test in the mildronate group was 89.26 ± 105.78 meters, while the placebo group patients had the mean value of 23.03 ±

Table 3.
Change in the absolute claudication distance during the treadmill exercise test comparing before (randomization visit) and after 24 weeks double-blind therapy by treatment groups

Index	Mildronate	Placebo	
Valid *N*	27	30	*p*-value
Minimum [m]	11.00	–67.00	= 0.026
Maximum [m]	661.00	352.00	
Mean [m]	231.22	126.67	
Std deviation [m]	179.02	120.72	

Table 4.
Absolute claudication distance at each visit by the treatment groups

Time	Index	ACD (m)		*p*-value
		Mildronate	Placebo	
Visit R	Valid *N*	27	30	
	Mean [m]	371	368	0.93
	Std deviation [m]	214	197	
Visit T4	Valid *N*	27	30	
	Mean [m]	456	422	0.678
	Std deviation [m]	241	226	
Visit T12	Valid *N*	27	30	
	Mean [m]	547	435	0.139
	Std deviation [m]	267	210	
Visit T24	Valid *N*	27	30	
	Mean [m]	602	494	0.169
	Std deviation [m]	295	234	
Visit PT	Valid *N*	25	28	
	Mean [m]	627	466	0.040
	Std deviation [m]	301	236	

57.73 meters. The difference between the treatment groups was significant (p-value = 0.025).

The mean value of the change in the ICD before and after 24 weeks of double-blind therapy during the treadmill test in the mildronate group was 123.93 ± 114.73 meters, while the placebo group patients had the mean value of 50.30 ± 62.56 meters. The difference between the treatment groups was significant (p-value = 0.033).

The mean value of the change in the ICD from visit T24 till one month after the discontinuation of the treatment (visit PT) during the treadmill test in the mildronate group was 24.88 ± 66.69 meters, while the placebo group patients had the mean value 10.61 ± 51.42 meters. The difference between the treatment groups was non-significant (p-value = 0.265).

Discussion

At the baseline, the patients of both treatment groups were comparable with respect to demographic data, disease anamnesis, medical history data and smoking habits. As seen in Table 4, functional capacity of patients in both investigated groups before treatment was similar – the ACD in the mildronate group was 371 meters, but in the placebo group – 368 meters.

Our data about the dynamics of the ACD and the ICD during the treatment should be used to test the hypothesis of superiority of mildronate, i.e. mildronate is or is not superior to placebo with respect to the treatment of intermittent claudication in patients with PAD.

Our investigation shows that mildronate effectively increases maximal walking distance in patients with PAD. The mean change in the ACD during the treadmill exercise test comparing the ACD before (randomization visit) and after 24 weeks of double-blind therapy was 231.22 (±179.02) meters in the mildronate group and 126.67 (±120.72) meters in the placebo group. The ACD difference between the treatment groups was significant (p-value = 0.026).

The effect of mildronate increases with the duration of treatment (Table 3 and Table 5), but the changes in the ACD before and after the treatment between the mildronate and the placebo groups becomes highly significant only after 12 weeks (p-value = 0.003).

The data about the change of the ICD after 24 weeks are similar (123.93 ± 114.73 meters in the mildronate group and the mean value of 50.30 ± 62.56 meters in the placebo group). The difference between the treatment groups was significant (p-value = 0.033). It must be noted that the pain-free walking distance also increases with the duration of mildronate treatment and after 12 weeks (Table 6) the ICD difference between the treatment groups becomes significant (p-value = 0.025).

The above data confirm the superiority of mildronate, i.e. the advantage of the treatment with mildronate (1 g/day) in combination with standard therapy for the improvement of exercise tolerance in patients with PAD over the treatment with placebo in combination with standard therapy.

Table 5.
Descriptive statistics for the change in the ACD [meters]

Variable		Treatment group		
		Mildronate	Placebo	
Change in the ACD, visit T4 – visit R	Valid *N*	27	30	*p*-value
	Minimum [m]	–55.00	–44.00	= 0.141
	Maximum [m]	380.00	313.00	
	Mean [m]	85.04	54.67	
	Std deviation [m]	93.44	82.31	
Change in the ACD, visit T12 – visit R	Valid *N*	27	30	*p*-value
	Minimum [m]	–38.00	–71.00	= 0.003
	Maximum [m]	599.00	338.00	
	Mean [m]	176.07	67.67	
	Std deviation [m]	154.85	89.69	
Change in the ACD, visit PT – visit T24	Valid *N*	25	28	*p*-value
	Minimum [m]	–201.00	–185.00	= 0.032
	Maximum [m]	195.00	129.00	
	Mean [m]	19.68	–31.43	
	Std deviation [m]	85.58	79.17	

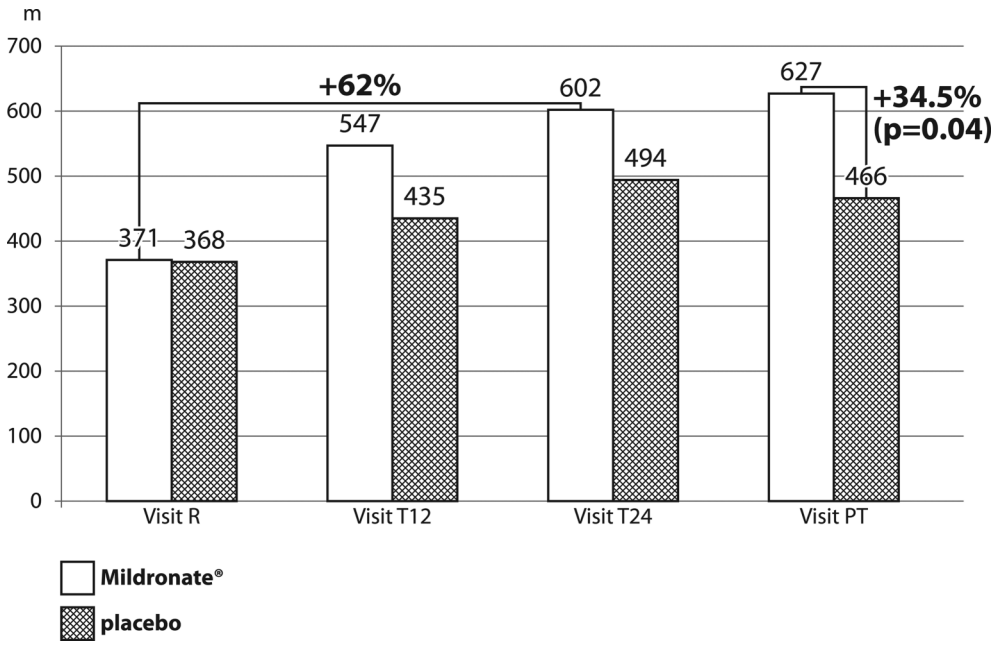

Figure 1. Absolute claudication distance during the treadmill test at the randomization visit (visit R), during the treatment course (visits T12; T24) and 1 month after the cessation of double-blind therapy (visit PT).

It was stated that even one month after the discontinuation of the treatment (visit PT) there was significant difference between the treatment groups regarding to the mean value of the change in the ACD (one month after the discontinuation of the treatment minus 24 weeks of double-blind therapy): in the mildronate group the mean change was 19.68 (±85.58) meters, in the placebo group it was –31.43 (±79.17) meters. The difference between the treatment groups was significant (*p*-value = 0.032).

This finding about the stabilization of increased exercise tolerance even during 1 month after the discontinuation of mildronate should be stressed in the context of long-term use of mildronate because the question of duration of treatment courses is still under discussion.

In our previous publication [7] it was shown that the use of mildronate in patients with coronary heart disease is safe and effective during the 12-month trial. However, in the routine practice more profitable for safety and also economical reasons is a drug, which could be administered

Table 6.
Descriptive statistics for the change in the initial claudication distance [meters]

		Treatment group		
		Mildronate	Placebo	
Change in the ICD, visit T12 – visit R	Valid *N*	27	30	*p*-value
	Minimum [m]	–56.00	–159.00	= 0.025
	Maximum [m]	440.00	113.00	
	Mean [m]	89.26	23.03	
	Std deviation [m]	105.78	57.73	
Change in the ICD, visit T24 – visit R	Valid *N*	27	30	*p*-value
	Minimum [m]	0	–106.00	= 0.033
	Maximum [m]	356.00	187.00	
	Mean [m]	123.93	50.30	
	Std deviation [m]	114.73	62.56	
Change in the ICD, visit PT – visit T24	Valid *N*	25	28	*p*-value
	Minimum[m]	–96.00	–75.00	= 0.265
	Maximum [m]	224.00	158.00	
	Mean [m]	24.88	10.61	
	Std deviation [m]	66.69	51.42	

for the long-term use with some breaks but without the loss of the treatment effect.

Obviously, mildronate meets these requirements. At least the results of this study have shown that the interruption of the mildronate course for 4 weeks without the loss of effect could be acceptable in case of long-term use of mildronate.

Therefore, the results of MI&CI completely confirm mildronate as a corrector of metabolism improving the exercise tolerance and quality of life of PAD patients.

These clinical consequences are supported by the theoretical considerations, experimental data and previous clinical findings about the action of mildronate.

For example, animal study results indicate that mildronate may be beneficial during myocardial ischemia and hypoxia because it facilitates glucose utilization and prevents the accumulation of fatty acid metabolites (long-chain acylcarnitine). Mildronate also reduces the beta-oxidation of free fatty acids that results from the inhibition of carnitine synthesis. Therefore, inhibition of beta-oxidation may be involved in the mechanism of the protective action of mildronate against the ischemia-induced metabolic derangement of skeletal muscle fibres.

Conclusions

1. This study reveals the advantage of the treatment with mildronate (1 g/day) in combination with standard therapy for the increase in exercise tolerance of patients with PAD over the treatment with placebo in combination with standard therapy.
2. Mildronate significantly increases both the absolute claudication distance (maximal walking distance) and the initial claudication distance (pain free walking distance) comparing to those in the placebo group.
3. One month after the withdrawal of mildronate, the effect of the drug on exercise tolerance remains at the same level as after 24 weeks treatment with mildronate.
4. Mildronate is an effective medicine for the treatment of patients with peripheral arterial disease improving their functional capacity and quality of life.
5. Treadmill testing is an objective way to quantify the grade of functional impairment and to evaluate the therapeutic effect of treatment – both ACD and ICD distances are reliable measurements with good reproducibility.

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