Cardiovascular Drugs and Therapy 1998;12:153–156

Effects of Magnesium Orotate on Exercise Tolerance in Patients with Coronary Heart Disease

K.-R. Geiss[1], N. Stergiou[1], Jester[1], H.U. Neuenfeld[2], H.-G. Jester[2]

[1]ISME (Private Research Institute for Sports, Medicine & Nutrition), Moerfelden, Germany; [2]Internal Medicine Clinic, District Hospital, Seligenstadt, Germany

Summary. **In a pilot study at 14 patients with coronary heart disease (CHD) and left-ventricular dysfunction (left ventricular enddiastolic volume [LVEDV] ≥ 100 ml), who actively participated in an ambulatory cardiac sports group, left ventricular endsystolic volume (LVESV), LVEDV and duration of exercise were analyzed by echocardiographic and ergometric tests. An initial workup was followed by a 4 week double blind treatment phase, in which magnesium orotate 3 x 1 g or placebo was given additionally to medication taken prior to the study. At the end of this phase a concluding workup was performed. Magnesium orotate decreased significantly (p = 0,016) LVESV, increased significantly (p = 0,035) EF, decreased in tendency (p = 0,054) LVEDV and increased significantly (p = 0,011) exercise duration. The study gives references to favourable effects of oral magnesium orotate to left ventricular function and exercise tolerance in patients with CHD.**

Cardiovasc Drugs Ther **1998:12**

Key Words. **Magnesium orotate-coronary heart disease-left ventricular dysfunction-exercise tolerance-pilot study**

In the rehabilitation of patients suffering from an acute myocardial infarction or coronary heart disease an ambulatory sports group ("phase III") is of central importance to the lives of patients after initial treatment in a primary care hospital ("phase I" defined by WHO, e.g. after a myocardial infarction, PTCA or CABG) and after that in rehabilitation clinics ("phase II"). The final goal of the third phase of rehabilitation is the definitive reintegration of the patient in everyday activities [1]. Appropriate drug and physiotherapeutic management are employed to minimize the risk of cardial deterioration of the cardiac situation and to economize cardiocirculatory function [2,3].

It has been observed repeatedly in clinical studies that administration of drugs containing magnesium leads to a highly significant improvement in cardiac, decompensation both in the phase of acute myocardial infarction and perioperative after CABG [4,5]. The "Limit-2-"-study especially showed a 24% reduction in hospital mortality in patients with suspected and proved acute myocardial infarction after intravenous application of magnesium [5].

These results give some evidence for efficacy of oral magnesium in patients with CHD and chronic congestive heart failure.

Administration of orotic acid, a precursor of pyrimidine bases and nucleic acids, showed on enhanced the synthesis of myocardial protein and increased content of ADP and ATP of the myocardium in animal experiments [6,7,8]. Clinical experience with orotic acid in patients with CHD and left ventricular dysfunction yielded in results indicating of improved myocardial contractility and blood supply.

The objective of our study was to evaluate the effects of regular intake of magnesium orotate on exercise tolerance in patients with CHD and, with regard to heart failure, to verify the possible beneficial effects caused by to improved contractility.

Methods

Patients

The study was conducted on 14 patients with CHD, who actively participated in an ambulatory cardiac sports group at least once a week. The patients were assigned to either of two comparable groups especially with regard to myocardial infarction, its localization and invasive or surgical interventional procedures (homogenous matching.) Inclusion criteria were CHD, proved by coronary angiography, single-vessel or multi-vessel disease with at least one high-grade stenosis (< 60%), with and without a history of myocardial infarction. A left ventricular enddiastolic volume (LVEDV) of at least 100 ml was required in cohocardiographic examination as evidence of impaired left ventricular function [9].

Exclusion criteria were angina at rest, impaired exercise tolerance in consequence of other medical conditions (e.g. arterial occlusive disease), cardiomyopa-

Address for correspondence: Dr. K.-R. Geiss, Private Research Institute for Sports, Medicine and Nutrition, Weingarten Strasse 2, 64546 Moerfelden, Germany

Received 22 October 1997; receipt/review time 29 days; accepted in revised form 10 March 1998

thies, heart defects, malignant hypertension, patients with cardiac pacemakers, a history of myocardial infarction, bypass surgery or PTCA within 3 months of the beginning of the study, and therapy with magnesium.

Study design

This study was carried out double blind and was controlled according to the GCP guidelines. The study was approved by the Institutional Review Board of the Landesarztekammer Hessen (Ethik-Kommission Nr.208/93). All patients gave their informed consent and were stratified in the two treatment groups of the study. An initial examination was followed by a 4-week treatment phase, in which daily 3 × 1g magnesium orotate or placebo was added to existing therapy. At the end of this phase a final examination was performed at the same daytime as initial examinations.

At the beginning of the study a Teflon indwelling catheter was inserted into a vein of the forearm to gain blood for chemical analysis. Thereafter, echocardiographic studies (Siemens Sono-line SL2) were done in rest to win parameters such as left ventricular enddiastolic and endsystolic volume (LVEDV, LVESV), cardiac output (CO), stroke volume (LVSV), and ejection fraction (EF).

Starting with a workload of 50 watts on a bicycle ergometer (Siemens EM 840) in sitting position the workload was increased by increments of 25 watts every 6 minutes until the individual maximum exercise capacity, or a level of 150 watts or a exercise time of 30 minutes was reached. Standard ECG loads were displayed continuously on a monitor screen, and a six-track printout (Hellige Multiscriptor EK 35) was obtained after each minute of exercise. After the exercise test was performed the patient rested for 10-minute recovery. Heart rate (absolute and mean data) was registered continuously during the entire observation period using a Sport Tester TM (Polar Elektro, Finland). The duration of the exercise test was determined. Blood pressure was taken by Riva-Rocci sphygmomanometry during exercise at the end of each minute.

Criteria for discontinuation

Exercise testing was discontinued if cardiac arrhythmias equivalent to or more severe than Lown III, complaints like angina, ST depression or elevations of 0,2 mV indicative to myocardial ischemia, or any of the other usual criteria for stopping developed.

Laboratory parameters

Blood glucose was assessed using the hexokinase method (commercial test kits, Reflotron TM, Boehringer Mannheim) in rest and in the 10th minute of recovery. The measurement of magnesium levels in the blood was carried out at rest before the start of the exercise test. Lactate levels (enzymatic color test PAP, Miniphotometer 8, Firma Dr. Lange, Berlin) were determined 12 minutes after beginning the exercise test, at the end of the exercise test, and 10 minutes after stopping the exercise test. If the exercise duration after treatment was longer than in the initial examination, lactat levels were additional determined at the discontinuation-time of the initial study for direct comparison.

Statistical analysis

Results of the test are presented as means ± standard deviation. The results were evaluated by the paired and unpaired Student's test within and between the treatment groups. The level of significance was defined as $p < 0,05$.

Results

Echocardiographic parameters (Table 1)

The analysis showed within the group of patients, treated with magnesium orotate, a significant ($p = 0,016$) decrease of LVESV, nearly significant ($p = 0,054$) decrease of LVEDV and significant ($p = 0,035$) increase of EF, whereas referring to LVSV there was no change.

Considering multiple testing the increase EF exceeds the significant borderline of significance ($p = 0,05$).

Within the group of patients, receiving placebo, there were no significant alterations of the echocardiographic parameters. Between the two groups of placebo and magnesium orotate there were no significant differences of the baseline values and the values after treatment.

Exercise duration (Table 2)

In the analysis the increase from 18,64 ± 4,97 to 19,64 ± 6,52 minutes in the placebo-group was not significant ($p = 0,207$), whereas the increase from 17,96 ± 5,83 to 22,64 ± 6,85 minutes in the magnesium orotate-group was significant ($p = 0,011$).

Between the groups, treated with placebo or magnesium orotate there was significant differences after the treatment phase neither in the intention-to-treat nor in the per-protocol-analysis.

Maximal rate-pressure product

Between the two groups, treated with placebo respectively magnesium orotate, there were no differences.

Laboratory parameters

Magnesium, glucose, lactate showed no significant alterations in the placebo- and magnesium-orotate-group.

Table 1. *Means and standard deviations of left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), stroke volume (LVSV), ejection fraction (LVEF) in the placebo and magnesium orotate groups before and after treatment*

Placebo group (n = 7)	LVEDV (mL)	LVESV (mL)	LVSV (mL)	LVEF (%)
Before treatment	122.00 ± 15.28	62.86 ± 10.40	59.57 ± 10.85	48.57 ± 6.40
After treatment	120.14 ± 23.62	65.0 ± 14.93	55.14 ± 14.30	45.86 ± 7.03
Significance (paired t-test)	$P = 0.82$	$P = 0.75$	$P = 0.42$	$P = 0.38$
95% confidence interval	− 29.69 / + 25.26	+ 17.58 / + 13.29	− 7.95 / + 16.81	− 4.36 / + 9.79

Magnesium-orotate group (n = 7)	LVEDV (mL)	LVESV (mL)	LVSV (mL)	LVEF (%)
Before treatment	130.71 ± 16.57	75.71 ± 16.99	55.0 ± 11.03	42.57 ± 9.11
After treatment	103.0 ± 25.28	50.43 ± 16.27	52.57 ± 11.59	51.71 ± 6.16
Significance (paired t-test)	$P = 0.054$	$P = 0.016$	$P = 0.71$	$P = 0.035$
95% confidence interval	− 0.58 / + 56.01	+ 6.63 / − 43.94	− 12.73 / + 17.59	− 17.37 / − 0.92

Discussion

Magnesium is involved in the function of about 300 enzymes essential to biosynthesis processes in energy metabolism [10,11]. In the "Limit-2"-study intravenous magnesium yielded to a 24% reduction of in-hospital mortality in patients with suspected and proved acute myocardial infarction.

Orotic acid, a precursor of pyrimidine bases nucleic acids with enhanced synthesis of myocardial protein and increased content of ADP and ATP of the myocardium, as shown in animal experiments [6,7,8,12] could lead to an improvement of left ventricular function and exercise tolerance in patients with CHD. In this study oral magnesium orotate lead to a decrease of LVESV, LVEDV, increase of EF and increase of exercise duration. But only the decrease of LVESV were significant (p = 0,016), whereas the decrease of LVEDV reached no significance level (p = 0,054)). Also there were no significant differences of the echocardiographic parameters between the treatment-groups. Exercise duration showed within the group a significant prolongation after treatment with magnesium orotate, but there was no significant change between the placebo- and magnesium orotate-group. Maximal rate-pressure product also showed no sinificant alteration between the groups.

Laboratory parameters remained unchanged by the treatments.

In conclusion, the hypothesis will be generated, that the administration of oral magnesium orotate can lead to improvement of left ventricular function and exercise tolerance. It should be taken in consideration that in comparison with other antianginous drugs with its benefits of magnesium orotate will not be outweighted by adverse events. This is a pilot study with a limit number of patients, who were participating in ambulatory sports groups and therefore of good efficiency. The results are therefore not respresentativ for all patients with coronary heart disease. Magnesium orotate or placebo was added to present antianginous therapy. Exercise testing was carried out with steps of long duration (6 minutes). Therefore the exercise duration is not comparable with studies, carried out with tread-

Table 2. *Means and standard deviations of exercise duration in the placebo and magnesium orotate groups before and after treatment*

	Exercise duration (minutes)	
	Placebo	Magnesium orotate
Before treatment	18.64 ± 4.97	17.96 ± 5.83
After treatment	19.64 ± 6.52	22.64 ± 6.85
Significance (paired t-test)	$P = 0.207$	$P = 0.011$
95% confidence interval	− 2.73 / + 0.73	= 7.85 /− 1.51

n=7.

mills. Significant improvements in the echocardiographic and ergometric parameters were seen only within but not between the treatment groups. Considering multiple testing the increase of EF was not significant. Further studies are necessary to prove the positive effects of oral magnesium orotate on left ventricular function and exercise tolerance in patients with coronary heart disease.

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