

# Magnesium orotate in severe congestive heart failure (MACH)

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Received 30 August 2007; accepted 17 November 2007

Available online 20 February 2008

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## Abstract

**Background:** Aim of this study was to evaluate adjuvant magnesium orotate on mortality and clinical symptoms in patients with severe heart failure under optimal cardiovascular medication.

**Methods:** In a monocentric, controlled, double-blind study, 79 patients with severe congestive heart failure (NYHA IV) under optimal medical cardiovascular treatment were randomised to receive either magnesium orotate (6000 mg for 1 month, 3000 mg for about 11 months,  $n=40$ ) or placebo ( $n=39$ ). Both groups were comparable in demographic data, duration of heart failure and pre- and concomitant treatment.

**Results:** After mean treatment duration of 1 year (magnesium orotate:  $364.1 \pm 14.7$  days, placebo:  $361.2 \pm 12.7$  days) the survival rate was 75.7% compared to 51.6% under placebo ( $p < 0.05$ ). Clinical symptoms improved in 38.5% of patients under magnesium orotate, whereas they deteriorated in 56.3% of patients under placebo ( $p < 0.001$ ).

**Conclusion:** Magnesium orotate may be used as adjuvant therapy in patients on optimal treatment for severe congestive heart failure, increasing survival rate and improving clinical symptoms and patient's quality of life.

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**Keywords:** Congestive heart failure; Magnesium; Orotic acid; Magnesium orotate; Adjuvant therapy

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## 1. Introduction

The medical treatment of chronic heart failure has made substantial progress during the last decades, thus improving symptoms as well as the long-term outcome of the disease. Nevertheless, mortality is still high, even under optimal cardiovascular treatment. Therefore, the application of any adjuvant substance seems to be justified to improve the long-term outcome of chronic heart failure and to increase the patient's quality of life. The cardiovascular effects of magnesium ions are well known for decades. In an epidemiological study it was shown that an increase of serum magnesium by diet could decrease the cardiovascular risk from 100% to 68% within 10 years [1]. The following study was performed to evaluate the additional benefit of oral adjuvant magnesium orotate. The anion of the test medication, orotate, is an intermediate of pyrimidine biosynthesis with cardioprotective effects summarised by several reviews [2–4].

## 2. Materials and methods

### 2.1. Study design

Prospective, randomized, double-blind, placebo-controlled monocentric study according to the Declaration of Helsinki, local legal regulations and GCP. It was approved by the local ethics committees and the patients gave their written informed consent.

### 2.2. Patients, treatment and observation periods

Male and female outpatients with severe congestive heart failure (NYHA IV) under optimal cardiovascular treatment and stable clinical condition in the age between 21 and 70 years were included. After screening, patients were randomised to study medication and inspected after 1, 6 and 12 months. In between, the patients were contacted by telephone. During month 1,  $3 \times 2$  tablets of study medication (1000 mg magnesium orotate per tablet or matching placebo) were administered, followed by  $3 \times 1$  tablet for months 2–12.

### 2.3. Outcome parameters, documentation and statistics

The primary outcome was the mortality rate within 12 months, secondary outcomes were the global impression of clinical condition as characterised by “improved”,

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“unchanged” or “impaired” and the NYHA state. Vital parameters and concomitant medication were controlled at each visit. All parameters were analysed by descriptive statistics. The comparison of the primary endpoint was performed by Fisher’s exact test, differences in the global clinical condition by  $\text{Chi}^2$ -test.

### 3. Results

#### 3.1. Demographic and basic clinical data

Both groups (placebo:  $n=39$ , magnesium orotate:  $n=40$ ) were comparable in age ( $62.9\pm 7.3/62.6\pm 6.9$  years), height ( $170.1\pm 4.9/170.6\pm 6.7$  cm) and weight ( $80.6\pm 8.8/82.3\pm 17.5$  kg). Heart rate ( $94.2\pm 19.9/91.0\pm 17.0$  beats/min), blood pressure ( $136.6\pm 25.2/82.1\pm 12.3$  vs.  $131.8\pm 22.1/82.0\pm 12.0$  mm Hg) and serum sodium ( $142.7\pm 3.3/141.0\pm 5.1$  mEq/l) were also comparable and did not change significantly during study duration, neither did thorax X-rays, ECG, echocardiography, hemoglobin and thyroid hormones.

#### 3.2. Causes of heart failure and basic treatment

All patients suffered from heart failure NYHA stage IV, most often caused by (rates placebo/magnesium orotate): myocardial infarction (67/73%), ischemic heart disease (51/48%) and hypertension (36/30%). Other causes were valve diseases, dilatative cardiomyopathy, pulmonary heart disease and hyperfunction of the thyroid. Concomitant cardiovascular medications were: diuretics (97.4/100.0%), ACE-inhibitors/AT1-antagonists (69/70%), regular nitrates (57.9/60.0%). Other cardiovascular med-

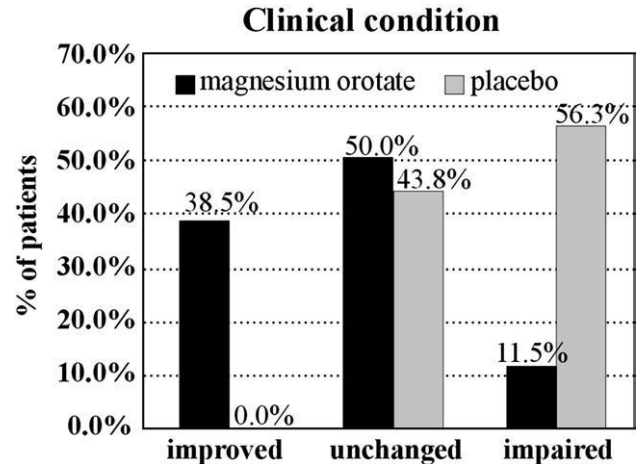


Fig. 2. Change of clinical condition after 12 months (basis: surviving patients with details to this question). Significant difference ( $p<0.01$ ) in the  $\text{Chi}^2$ -test.

ications were betablockers, digitalis and acetylic salicylic acid.

#### 3.3. Effect of magnesium orotate on mortality

At the last visit (after  $364.1\pm 14.7$  or median 367 days in the magnesium orotate group and after mean  $361.2\pm 12.7$  or median 364 days in the placebo group), 42 patients (47.2%) were still alive. Three patients of the placebo group started to take magnesium orotate after a time span of 1–6 months, thus being treated with magnesium orotate for more than 6 months. Therefore, these patients were evaluated in the magnesium orotate group. 11 patients (5 placebo and 6 magnesium orotate patients) were excluded from mortality evaluation, because the time span from start to the last visit was less than 11 months. In the remaining “as treated” groups, 28 of 37 patients were still alive in the magnesium orotate group and only 16 of 31 patients under placebo (Fig. 1,  $p=0.0458$  Fisher’s exact test).

#### 3.4. Effect on clinical condition

The clinical condition under magnesium orotate in most cases improved or remained unchanged, whereas under placebo in the majority the clinical situation was impaired (Fig. 2,  $p<0.001$   $\text{Chi}^2$ -test). Five patients of the magnesium orotate group changed from NYHA IV to NYHA III during treatment, whereas in the placebo group no change of the NYHA stage occurred.

#### 3.5. Tolerability

In each group, 3 patients had undesired effects: Intolerance of the study medication (one patient in each group), vomiting and acute cholecystitis (placebo) or high level of creatinine, increased hepatic enlargement and pain (magnesium orotate).

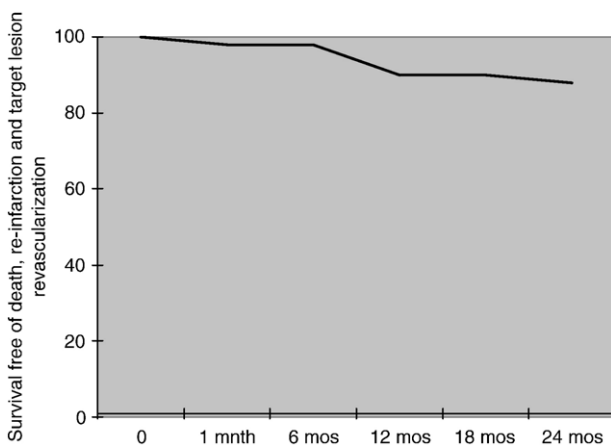


Fig. 1. Survival rate after 12 months for magnesium orotate compared to placebo. \*Significant difference ( $p<0.05$ ) in the Fisher’s exact test.

#### 4. Discussion

The results of this study support former epidemiologic studies in which for 7–37% of patients with heart failure a magnesium deficit was found [8,9] caused e.g. by reduced absorption, neurohormonal disturbances and/or increased magnesium excretion. Furthermore, cardiovascular medication like diuretics and digitalis may enhance the magnesium deficit. The determination of serum magnesium is an unreliable method to estimate the magnesium status of a patient, because most magnesium is bound within cells and tissues. Therefore, a test wise application of magnesium in patients at risk will confirm a magnesium deficit by the clinical result, i.e. improvement of symptoms like in this study. The significant higher survival rate and the improvement of clinical condition in the magnesium orotate group present good arguments to use magnesium orotate as adjuvant therapy in patients with severe heart failure. Patients in NYHA stage IV are more or less completely dependent on the caretaking of relatives or nurses. A change to NYHA stage III, as was shown for some patients in this study under magnesium orotate, reconstitutes a certain degree of independence and improves quality of life considerably. This is especially impressive considering the fact that the patients were under optimal cardiovascular

treatment and other alternatives of treatment did not exist. Finally, the excellent tolerability of magnesium orotate should facilitate the decision for this adjuvant therapy option. To reassure these results under confirmative conditions, higher patient numbers are necessary.

#### Acknowledgements

We thank Woerwag Pharma GmbH & Co. KG, Boeblingen, for support of this study.

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