Total Magnesium Concentrations in Serum and Erythrocytes before and after Treatment with Magnesium L-Aspartate Hydrochloride

Reference to Clinical Syndroms*

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Zusammenfassung

461 Patienten mit verschiedenen Symptomen, welche auf ein Magnesiumdefizit zurückgeführt werden könnten, wurden während einer mittleren Behandlungsdauer von 8.5 Wochen mit einer täglichen Dosis von 15 mmol Magnesium L-Aspartat hydrochlorid behandelt. Die Symptome wurden nach ihrer Intensität klassifiziert. Die Magnesium-Gesamtkonzentration im Serum und in den Erythrozyten wurde vor und nach der Behandlung von demselben Laboratorium bestimmt (Atom Absorptions Spektrometrie (AAS).

In jeder Gruppe von klinischen Symptomen wurde eine gewisse Reduktion der Intensität nach der Behandlung beobachtet. Andererseits zeigten die Magnesiumkonzentrationen im Serum und in den roten Blutzellen nur geringfügige Veränderungen infolge der Therapie. Die aufgeschlüsselte Analyse der Beziehung zwischen der Intensität der klinischen Symptome und den Magnesiumspiegeln zeigte für gewisse Gruppen eine schwache Korrelation.

Summary

461 patients with various symptoms supposed to be due to magnesium deficiency were treated with daily dosis of 15 mmol magnesium L-aspartate hydrochloride trihydrate ** over a mean period of 8.5 weeks. The intensity of their symptoms was graded and total magnesium levels in serum and red blood cells were measured (AAS technique, one single laboratory) before and after treatment.

For each group of clinical symptoms studied some reduction in intensity after treatment could be observed. On the other hand concentrations of magnesium in serum and erythrocytes showed only slight changes during therapy. A more detailed analysis looking at the relation between clinical symptoms and magnesium levels revealed a rather poor correlation.

Résumé

Une série de 461 sujets présentant des symptômes variés supposés relever d'un déficit en magnésium ont été traités avec une dose journalière de 15 mmol de chlorure de magnésium L-aspartate pendant des périodes dont la moyenne a été de 8.5 semaines. L'importance de leurs troubles a été quantifiée par rapport à une échelle et le magnésium total sérique et globulaire ont été mesurés (par spectrophotométrie d'absorption atomique effectuée dans un même site) avant et après traitement. Pour chacun des groupes de signes clinique étudiés une certaine diminution de leur importance a été observée après traitement. D'un autre côté les modifications des concentrations de magnésium ne sont que très peu modifiés sous traitement. Une analyse plus approfondie recherchant une relation entre signes cliniques et concentrations de magnésium n'a mis en évidence que de très faibles corrèlations.

Introduction

Magnesium salts have been widely accepted for the treatment of various conditions supposed to be due to some sort of magnesium deficiency. For many years the beneficial effects of oral magnesium supplementation were judged by clinical observation rather than by a clear diagnosis of magnesium deficiency, the latter being difficult to diagnose. The newly available possibility to measure magnesium concentrations in biological samples with great accuracy by means of atomic absorption spectroscopy (AAS) makes it possible to assess magnesium status more precisely. The determination of magnesium ions in serum and red blood cells are now used with increasing frequency. Let alone hospitalised patients with severe electrolyte abnormalities due to intestinal disorders, diabetes, drugs such as diuretics or antibiotics, alcohol abuse, toxaemia and eclampsia during pregnancy and delivery, let alone all these conditions, the question remains how far many of the minor disturbancies encountered in daily practice can or must be related to overt hypomagnesemia.

The present study was undertaken to compare in a larger group of otherwise healthy subjects the severity of symptoms and total magnesium levels in serum and red blood cells before and after oral treatment with magnesium L-aspartate hydrochloride for several weeks and to look for changes and correlations of these analytical values in statistical terms.

Subjects and Methods

This study was designed as a multicenter open trial accepting patients presenting with one or more symptoms usually attributed to magnesium deficiency or supposed to benefit from magnesium supplementation. Patients having impaired renal function or known endocrinal disorders were ex-

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Tab. 1: Symptoms reported and questioned.

Calf cramps	Irritable Bowel Syndrome
Restless legs	Angina pain
Tachycardia	Insommnia
Ectopic beats	Migraine
Spasmodism	Dysmenorrhoea

Graduation: Slight (1), moderate (2), severe (3)
Number of symptoms reported: 2 157

Tab. 2: Two-way frequency table of the scored subjective intensity of symptoms before and after treatment. The total of 2 157 symptoms equals the sum of symptoms of the population (rows 1–3; before treatment).

After Treatment	0	1	2	3	
1	411 18.6 %	232 10.5 %	11 0.5 %	0 0 %	654
2	356 16.1 %	301 13.6 %	117 5.3 %	11 0.5 %	785
3	238 10.8 %	299 13.5 %	126 5.7 %	55 2.5 %	718
	1 005	832	254	66	

Tab. 3: Changes in intensity of symptoms after 8 weeks of therapy with 15 mmol magnesium L-aspartate hydrochloride. Total of 2 157 symptoms reported.

N	%	Symptoms
1 005	46 %	disappeared
726	34 %	amelioration
404	19 %	unchanged
22	1 %	worse

cluded as well as patients receiving diuretics. A total of 271 doctors in general practice were involved. For each patient entering the trial his symptoms were graded as mild, moderate or severe by the treating practitioner. Treatment with an oral dose of 15 mmol magnesium L-aspartate hydrochloride trihydrate was then started. There was one clinical visit after 3 weeks and the final examination after 8 to 9 weeks where the intensity of symptoms was again scored, side effects recorded and an overall valuation of the medication given by the patient and the treating doctor.

Before and after 8 weeks of therapy venous blood samples were collected and total concentrations of magnesium ions in serum and red blood cells measured according to the candidate reference method of *Külpmann* et al. [1] using an atomic absorption spectrophotometer. To guarantee comparable results all analytical essays were performed in the same laboratory, using the same method (Laboratoire Monnier et Spoerri SA, CH-1206 Geneva).
For statistical evaluations the SAS software package running on an IBM 3033 and 3083 computer was used. The test for normality of the frequency distribution is exhibited by the Shapiro-Wilk test implemented in the univariate procedure of the SAS statistical package as well as the calculation of skewness and curtosis [2]. In our statistical evaluation T values were computed according to Student's t-test procedure for comparison of means.

Results

512 patients entering the trial a total of 461 could be evaluated. There were 140 men (mean age 50.8 years) and 321 women (mean age 49.1 years).

Symptoms
The ten symptoms given in tab. 1 were recorded and asked for in each patient. They were scored as slight [1], moderate [2] or severe [3]. It is obvious that some of these symptoms are quite closely related to each other. For instance tachycardia and ectopic beats or calf cramps and restless legs. As all patients were questioned about all symptoms in most cases more than one symptom had to be recorded. In our evaluation we had therefore to deal with a total of 2 157 symptoms each graded 1 to 3 which means about 4.6 symptoms per individual. In tab. 2 each symptom was allocated in one square taking into account the intensity before and after treatment with the oral magnesium preparation. The results are again summarised in tab. 3. In this presentation it becomes quite clear that treatment with magnesium salt leads to an overall improvement of symptoms of any intensity.

Biochemical analysis
Concentrations of total magnesium ions in serum and red blood cells were measured by the AAS method before and after therapy. The mean values with one standard deviation and the ranges are given in tab. 4. As far as frequency distribution was concerned no significant deviation from normality could be observed whereas in both biological samples a slight increase of magnesium was noticed which was in the case of serum even statistically significant. But the very small difference of only 0.018 mmol/l has to be noticed in this case.
In fig. 1 and 2 the values of total magnesium before and after therapy are plotted against each other for serum and erythrocytes. Both show a very even distribution over a wide range but it can also be noticed that not only increases of magnesium levels take place during treatment in some cases but also decreases could be observed. The fact that even high levels of magnesium

Tab. 4: Concentrations of magnesium ions in serum and red blood cells before and after therapy. Mean ± SD.

n = 461	Treatment		Diff	P > |T|
	before	after		
Serum mmol/l	0.867 ± 0.102	0.885 ± 0 .106	0.018	0.005
Range	0.54–1.23	0.64–1.24		
Red Blood cells mmol/l	1.979 ± 0.205	1.993 ± 0.211	0.014	0.05
Range	1.34–2.78	1.06–2.67		

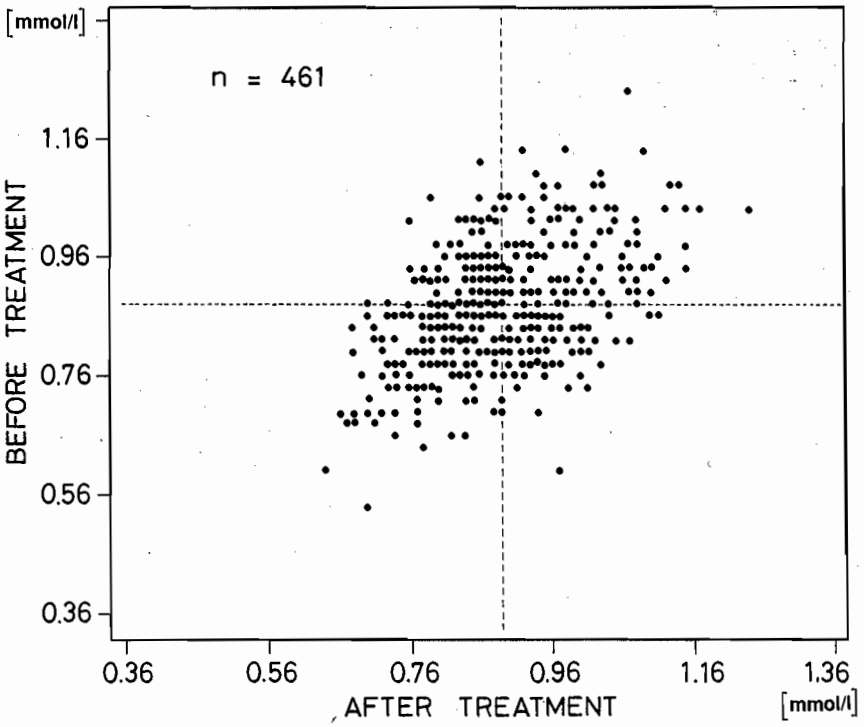

Fig. 1: Total magnesium concentrations in serum evaluated by AAS. Plot of single values before and after treatment.

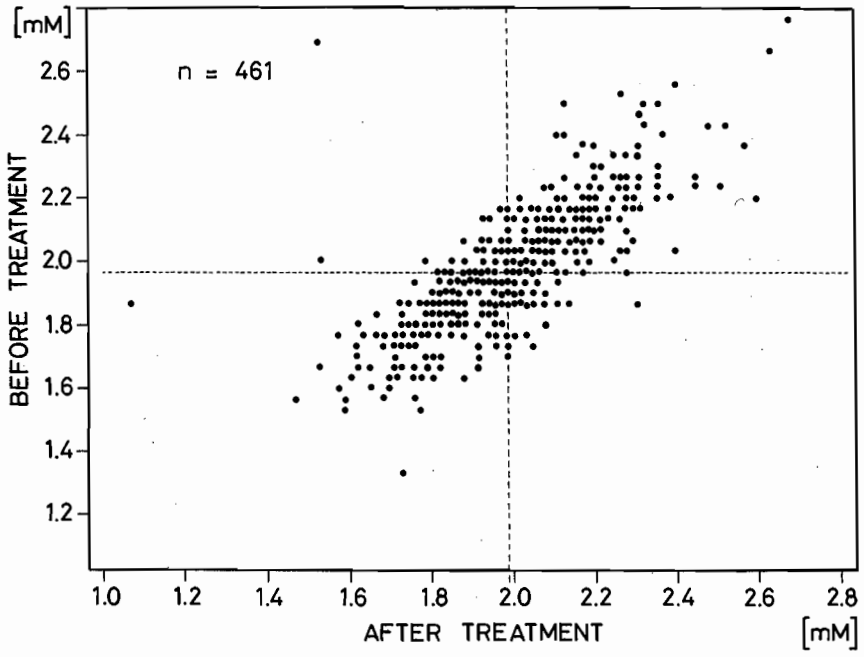

Fig. 2: Total magnesium concentrations in red blood cells evaluated by AAS. Plot of single values before and after treatment.

(> 1.0 mmol/l) may be decreased during treatment has to be noticed and is in our view not due to an artefact considering the significant correlation between the values before and after treatment. In fig. 3 the total magnesium concentrations before therapy are shown in serum versus erythrocytes for each patient. The values after treatment are not presented because they show absolutely the same picture. There is no visible correlation between these two parameters.

Clinical symptoms and magnesium levels

To answer the question about any relation between magnesium levels and clinical manifestations two groups were taken at random, one with 22 patients having serum magnesium levels of less than 0.7 mmol/l and a second group of 53 patients having high levels of more than 1.0 mmol/l. Statistical analysis showed no significant difference between the two groups and the total of all patients participating in the trial with reference to the number and severity of symptoms.

Discussion

In the present study a large number of patients presenting with one or more symptoms usually related to magnesium deficiency was studied. Every patient was questioned about ten symptoms and therefore some additional symptoms were reported even if the patient did not consider them as very important for his well-being. Not surprisingly an average of 4.6 symptoms per patient were recorded, some of them of mild or moderate intensity. After several weeks of therapy with magnesium L-aspartate hydrochloride a very impressive improvement of symptoms was reported. 48 % of symptoms had disappeared altogether, there was an amelioration reported for 726 symptoms whereas 404 remained unchanged and only 22 symptoms were considered more severe than before therapy.

It must be admitted that this trial was not placebo controlled because our main emphasis was put on magnesium concentrations in serum and erythrocytes and their possible changes during therapy, these determinations being not influenced by a double blind set up. Nevertheless taking into account a placebo effect which is undoubtedly always present in such studies the clinical

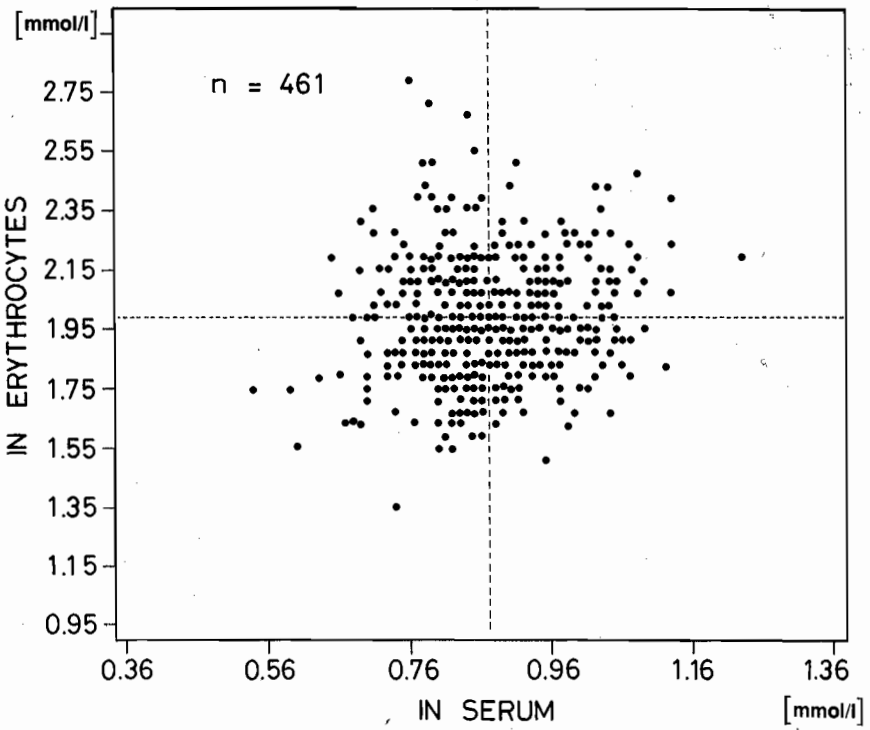

Fig. 3: Plot of single values of magnesium concentrations in serum versus erythrocytes before treatment. Both axes are scaled by multiples of the SD around the mean values of 0.867 mmol/l for serum and of 1.979 mmol/l for erythrocytes.

results in our 461 patients are convincing in every respect.

Due to the fact that hospitalised and otherwise severely ill patients were excluded not the whole range of indications for magnesium therapy was covered by the ten symptoms recorded in this study. Conditions such as myocardial infarction, life threatening arrhythmias or acute obstetrical problems were excluded as well as chronic alcoholism, severe nutritional disorders etc. and therefore the subjects in our survey represented the otherwise healthy patients with minor pathology and rather discomfort than overt disease. Taking this into account the range of magnesium concentrations in serum and erythrocytes was already quite wide in the untreated patients varying from 0.54 to 1.23 mmol/l and 1.34 to 2.78 mmol/l respectively and covering the so-called hypo-, normo-and hypermagnesaemia. As the symptoms encountered were evenly distributed over the whole range the question rises if clinical symptomes can and should be related at all to magnesium levels in biological samples in decision making for magnesium therapy. After several weeks of magnesium therapy there was a clear improvement of the clinical situation in most patients but virtually no related change in individual serum and erythrocyte levels of magnesium. From fig. 1 and 2 it becomes obvious that individual magnesium levels show only minor changes due to treatment whereas the variation between all individuals of our population is rather important. Furthermore the statistically significant increase in mean serum levels of only 0.018 mmol/l is undoubtedly due to the high analytical standard of the AAS procedure and the important number of samples but is by itself far too small to be also valid for an individual view of one single patient and lacks clinical importance completely. From earlier studies we know that the difference to be observed in between two tests in one single individual has to be in the order of 0.14 mmol/l to reach the level of 95 % significance [3]. This is about 8 times more than the difference of the mean values found in our population.

Bearing in mind the life span of 3 months of red blood cells the period of observation was extended beyond 8 weeks for a small group of patients. The results will be the goal of a later report.

From the present study we conclude that:

1. Oral treatment with magnesium L-aspartate leads to a marked improvement of ten symptoms investigated.
2. Clinical symptoms are poorly related to magnesium levels in serum and erythrocytes.
3. Magnesium determinations before magnesium therapy are of little help in assessing the nature of symptoms.
4. Several weeks of treatment with magnesium changes magnesium levels in serum in a statistically significant way, however these changes are clinically not relevant. The mean red blood cell magnesium content remains unchanged after 8 weeks.

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