Excretion of magnesium and calcium after a single dose of two magnesium preparations in a cross-over trial

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Zusammenfassung

Die intestinale Resorption von Magnesium kann aus der renalen Elimination berechnet werden, wenn die endogenen Magnesiumspeicher des Organismus aufgefüllt sind. Diese wurden bei 16 gesunden jungen männlichen Probanden durch eine tägliche Mehraufnahme von 300 mg Magnesium über drei Tage aufgesättigt. Danach wurde den Probanden im Cross-over-design eine Testdosis von jeweils 600 mg Magnesium entweder als Magnesiumoxid oder Magnesiumhydroxidcarbonat verabreicht. Nach den jeweiligen Testtagen konnte ein leichter Anstieg des Plasma-Magnesiums beobachtet werden. Der Plasma-Calcium-Spiegel stieg ebenfalls leicht an.

Das intraerythrocytäre Magnesium spielte bei der Magnesiumhomöostase keine Rolle. Die Magnesiumausscheidung war in beiden Testgruppen signifikant erhöht am ersten Testtag, die Unterschiede hinsichtlich des verabreichten Präparates nicht signifikant. Die Ausgangswerte der Magnesiumausscheidung wurden nicht bereits 24 sondern 72 Stunden nach Aufnahme der Testdosis wieder erreicht. Die berechneten Variationskoeffizienten der Magnesiumausscheidung waren nicht vom Präparat sondern nur vom Testtag abhängig. Dies kann möglicherweise durch eine zu kurze wash-out-Phase (5 Tage) erklärt werden. Die Ergebnisse beim Calcium sind den Magnesiumwerten ähnlich, auch hier werden die Ausgangswerte der Ausscheidung frühestens 72 Stunden nach Testdosisaufnahme wieder erreicht.

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Summary

The intestinal absorption of magnesium can be calculated from renal elimination once magnesium stores have been saturated. Endogenous magnesium pools of sixteen healthy male volunteers were filled up through an additional daily dose of 300 mg magnesium for three days. Thereafter, a single dose of 600 mg magnesium in the form of magnesium oxide or magnesium hydroxide carbonate was given in a cross over trial.

After ingestion of a total of 600 mg magnesium, there was a slight transitory increase in the plasma magnesium level. Plasma levels of calcium were also increased but to a lesser degree. Magnesium within the erythrocytes appeared not to be involved in magnesium homeostasis. Magnesium excretion increased significantly in both test groups on the first test day. The differences between results obtained from the two magnesium preparations (test and reference) were not statistically significant. The basal rates of magnesium excretion were clearly not reached within 24 hours after ingestion of the test dose of magnesium and took at least 72 hours to stabilise on the former level. The scatter of the readings obtained for magnesium excretion on the two test days demonstrated clearly that differences in calculated bioavailability were dependent on the day of testing rather than the preparation ingested. This could mean that the wash-out phase (five days) between the two test days was too short. The course of changes in calcium excretion is similar to that obtained for magnesium. Basal rates of calcium excretion were also not reached until 72 hours after ingestion of the test dose of magnesium.

Introduction

No generally accepted method has yet been established for determination of the bioavailability of magnesium assimilated from supplementary magnesium products.

Classical methods for calculating the absolute or relative bioavailability of a substance are based on measurement of the concentrations of that substance in the blood or plasma at various intervals after its administration, and evaluation of the time curves thus obtained [3–5].

In the case of magnesium the method cannot be used unmodified, since plasma levels of magnesium are subject to an effective homeostasis.

In 1985, *Lücker* and *Nestler* [19] therefore suggested the possibility of determining the relative bioavailability of magnesium from measurements of magnesium excretion. This method is based on the observation of *Nicar* and *Pak,* 1982 [23], that when magnesium stores within the body are saturated any additional magnesium absorbed will be excreted in the urine within 24 hours. However, in preliminary trials (*Schlebusch* et al., unpublished data) it emerged that after saturation of the magnesium stores by a total daily intake of 650 mg magnesium, magnesium excretion remains high for a few days after discontinuation of the supplementary dose. In the present investigation the magnesium stores of the volunteers were therefore saturated by their taking 300 mg supplementary magnesium for three days. This was followed by a stabilising period of 7 days in which they maintained a dietary intake of 350 mg magnesium per day, as recommended by the Deutsche Gesellschaft für Ernährung (DGE) (German Association for Nutrition).

The preliminary phase of 10 days served, therefore, to ensure saturation of the magnesium stores and to allow recovery of a steady basal excretion rate.

In the cross-over trial described here, 16 volunteers were given a single dose of 600 mg magnesium after saturation of their magnesium stores.

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Excretion was monitored for three to five days after administration of the test dose.

Material and Methods

Pharmaceutical preparations administered:

Product A:

Biogenis capsules manufactured by Bayer-AG, Wuppertal

1 capsule contains 500 mg tocopherol acetate and 250 mg magnesium oxide (= 150 mg magnesium)

Product B:

Magnesium hydroxide carbonate manufactured by E. Merck, Darmstadt

Product No. 5829

1 gram contains 240 mg magnesium

Preparation given prior to the trial to saturate the endogenous magnesium stores:

Magnesium Diasporal N manufactured by Protina GmbH, Ismaning

Active agent: Magnesium citrate

5 g of granules contain 296 mg magnesium.

Product A was taken in capsule form with 200 ml of water.

The reference substance (product B) was in powder form, while the preparation used to saturate the magnesium pools was granulated. Both were taken, dissolved in 200 ml of water.

Test Persons

Sixteen healthy male volunteers between the ages of 23 and 33 participated in the experiment (for demographic data see table 1), written informed consent was given by the volunteers before starting the trial. None of them was on long-term medication. Blood and urine samples were taken and analysed for routine haematological and clinical chemical parameters before and after the trial. All results remained within their respective normal ranges. The test group was limited to male volunteers in order to exclude any possible influence of menstrual cycle hormones, the treatments were well tolerated by all of the volunteers, none of them suffered under diarrhea. During the trial all volunteers were ambulatory, not kept in a ward.

Collection and analysis of samples

Heparinised blood samples were centrifuged immediately after drawing (3000 g, 10 min.), and the supernatant was frozen at –20°C for subsequent analysis.

Erythrocytes were washed three times in physiological saline and lysed by adding distilled water. After centrifugation to remove cell detritus, the samples were frozen at –20°C.

All urine samples were obtained by spontaneous micturition, acidified and likewise frozen at –20°C. Calcium and magnesium concentrations were determined by atomic absorption spectrometry [26].

Experimental design and test conditions

The trial was divided into two stages: A **preliminary phase** (days 1-10) and the actual **test phase** (days 11-22). During the **test phase,** one days 14 or 20, the volunteers received either the test product or the reference substance.

Throughout both phases the volunteers kept to a strict diet. They were able to calculate the magnesium content of various foods by means of a food substitute table. For the duration of the trial all participants were instructed to maintain a dietary intake of 350 mg (14.4 mmol) magnesium per day (+/– 5%) according to DGE-specifications.

Preliminary Phase

The preliminary phase lasted 10 days altogether (days 1-10).

Nor urine or blood samples were taken at this stage. The volunteers kept to a strict diet (according to DGE specifications concerning magnesium intake) and took 350 mg magnesium (+/– 5%) per day with their meals. On the first three days they were given an additional 300 mg (12.3 mmol) magnesium each morning, in the form of granulated magnesium citrate, to saturate their endogenous magnesium stores.

Test Phase

The test phase lasted altogether 12 days (days 11-22). This period, was subdivided into three stages **(Phases I-III),** each of which was run twice. During **Phase I,** which lasted 3 days, 350 mg (14.4 mmol) magnesium were taken per day as part of the diet and urine samples collected over 24-hour periods.

Phase II was the test day itself when either the test or reference product (600 mg/24.7 mmol) was ingested at 8 a.m. on an empty stomach. The first meal of the day was taken two hours later, at 10 a.m. Blood samples were taken at 8, 8.30, 9, 10 and 12 a.m. and 6 p.m.

The dietary intake corresponded to that on the other days of the test phase (350 mg magnesium). Thus, the magnesium intake was 171.4% higher than the daily intake at any other time during the test phase.

In **Phase III** (washing out phase) the volunteers kept to a standard diet for two days, collected 24 hour-urine and came in at 8 a.m. each morning, without having eaten, for blood sampling.

Phases I-III were each run twice so that

Tab. 1: Demographic data of the volunteers before starting the trial. Initial values from day 11.

Test-person	Age	Weight (kg)	Initial plasma magnesium (mmol/l)	Initial plasma calcium (mmol/l)	Initial urine magnesium excretion mmol/24 h	Initial urine calcium excretion mmol/24 h
1	27	71	0,81	2,20	5,64	2,89
2	23	67	0.82	2,65	5,25	4,04
3	33	82	0,77	2,63	6,25	7,56
4	23	87	0,76	2,51	5,06	7,28
5	24	81	0,74	2,21	5,93	8,86
6	25	79	0,68	2,66	3,62	4,28
7	23	76	0,89	2,20	4,28	2,22
8	26	73	0,78	2,60	5,00	5,66
9	31	69	0,77	2,56	8,47	7,45
10	30	88	0,79	2,48	5,41	6,18
11	27	84	0,81	2,58	3,81	4,99
12	29	87	0,69	2,70	4,49	2,65
13	26	68	0,81	2,15	5,63	5,50
14	29	70	0,79	2,20	5,46	3,59
15	28	74	0,81	2,66	3,63	3,81
16	32	77	0,88	2,58	4,46	4,06

both products could be tested in a cross-over trial.

Results

Figure 1 shows the mean values for excretion of magnesium in 24-hour urine, obtained from volunteers of groups 1 and 2. Excretion was markedly increased on days 14 and 20 (see arrows), but it was also clear that the high rate of excretion on day 14, the first test day, had not normalised by the following day. Surprisingly, this effect is even more marked on the second test day (day 20). Statistical evaluation of the results revealed that the scatter of values measured in the two groups on the first test day was significantly lower than that on the second test day, and was independent of the product ingested (table 1).

Tab. 2: Scatter of individual results (coefficient of variation) for magnesium excretion on the two test days (absolute values: 6,70 and 6,43 mmol/24 h group A and 6,91 and 5,99 mmol/24 h group B).

	First Test Day	Second Test Day
Group 1	15.5%	24.7%
Group 2	13.7%	27.7%

Tab. 3: Excretion rates of administered magnesium (absolute values: 1,51; 2,74; 1,24 and 2,13 mmol group A; 1,69; 2,44; 0,77 and 2,60 mmol group B).

	Test Day 1		Test Day 2	
	a	b	a	b
Group 1	6.11%	11.09%	5.02%	8.62%
Group 2	6.84%	9.88%	3.12%	10.53%

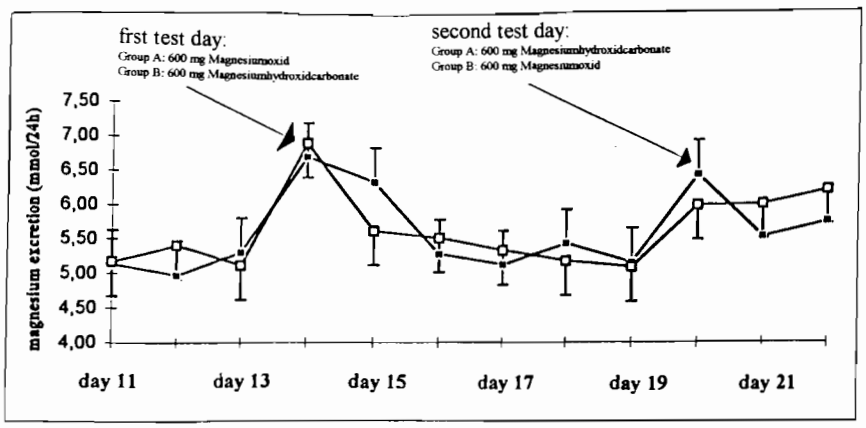

Fig. 1: Magnesium excretion in 24hour urine. Means and standard deviations for both groups, ■ = Group A, □ = Group B.

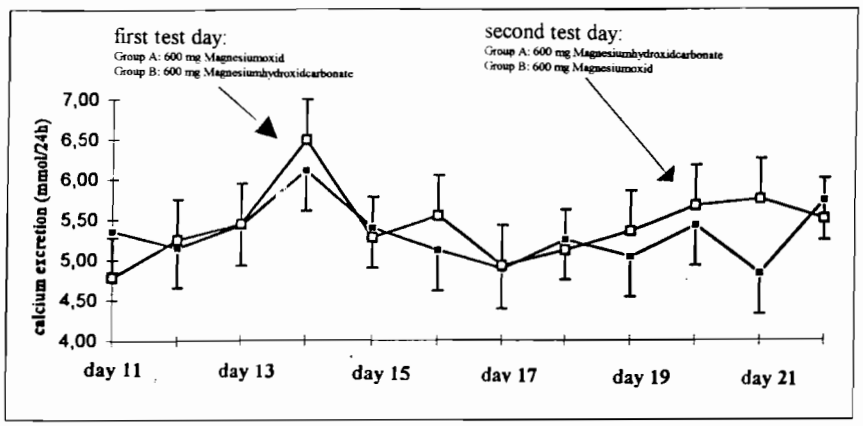

Fig. 2: Calcium excretion in 24-hour urine. Means and standard deviations for both groups, ■ = Group A, □ = Group B.

Two different methods were used for the calculation of increased excretion. Excretion remained constant and was identical within the two periods, days 11–13 and days 17–19, averaging 5.19 mmol/24 hours for Group I and 5.22 mmol/24 hours for Group 2.

a) Using the method of *Lücker* and *Nestler,* 1985 [19], whereby inceased excretion is calculated from the difference between the basal excretion level and excretion on the test day, the mean values obtained for Group 1 were 1.51 mmol on the first and 1.24 mmol on the second test day, while the corresponding values for Group 2 were 1.69 mmol and 0.77 mmol.

b) When measurements/samples from two days after each test day are also taken into consideration (days 15 and 16, or 21 and 22 respectively) for calculation of increased excretion, Group 1 has a mean level of 2.74 mmol on test day 1 and 2.13 mmol on test day 2, while Group 2 has 2.44 on the first and 2.60 mmol on the second test day.

The following rates of excretion were calculated from results obtained with a test dose of 24.7 mmol.

We attempted, without success, to reduce the scatter in the values obtained for magnesium excretion by relating the figures obtained to creatinine excretion.

This only reduced the values from group 2 on the second test day; the scatter of values of group 1 on both test days and group 2 on test day 1 were, in fact, greater when related to creatinine elimination (table 3).

Figure 3 shows magnesium levels in the plasma. A marked rise in plasma levels can be seen over the two test days in both groups, peaking two hours after administration of the test dose and fall-

Tab. 4: Scatter of individual results (coefficient of variation) for magnesium excretion on the two test days, after correction for creatinine excretion rates (absolute values: 3,68 and 3,43 mmol/24 h group A; 3,68 and 3,50 mmol/24 h group B).

	Test Day 1	Test Day 2
Group 1	20.9%	30.0%
Group 2	17.9%	23.1%

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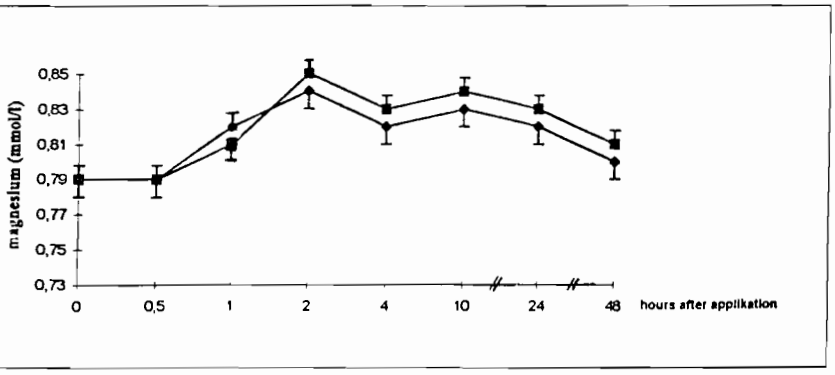

Fig. 3: Magnesium levels in plasma after oral application of 600 mg magnesium. Means and standard deviations for both products, ◆ = Product A, ■ = Product B.

Table 5: Magnesium concentration within erythrocytes (mmol/l).

Group		Mean	Median	S.D.	Min.	Max.
1	fasting	1.68	1.69	0.17	1.40	2.02
	0.5 h	1.71	1.77	0.20	1.21	2.00
	1 h	1.74	1.70	0.21	1.45	2.25
	2 h	1.68	1.70	0.17	1.26	1.95
	4 h	1.74	1.77	0.26	1.13	2.14
	10 h	1.78	1.80	0.23	1.39	2.16
2	fasting	1.78	1.78	0.20	1.47	2.24
	0.5 h	1.75	1.77	0.18	1.38	2.09
	1 h	1.72	1.72	0.18	1.41	2.03
	2 h	1.73	1.72	0.20	1.41	2.05
	4 h	1.74	1.78	0.16	1.48	2.05
	10 h	1.81	1.76	0.20	1.57	2.24

ing again after another two hours. However, after ten hours, serum concentrations had still not returned to their original level in either group or on either of the test days.

Table 4 shows the concentrations of magnesium within the erythrocytes.

Over the test days, the mean levels of magnesium within the erythrocytes showed no marked variations in either group.

Figure 2 shows the mean values for calcium excretion in 24-hour urine. A distinct peak is seen on the first and another small rise on the second test day in both groups.

Unlike the data for magnesium elimination, relating the calcium excretion values to creatinine does not significantly alter the variation coefficients (data not shown).

Discussion

Figure 1 shows that, as in the preliminary experiments mentioned earlier, the magnesium absorbed was not all excreted within 24 hours. Magnesium elimination remained higher than the basal rate for 48 hours after each of the two test days [1].

Schlebusch et al. (1992) [28] found that magnesium excretion on the test day was increased to 1.84 mmol for the test product and 1.56 mmol for the reference product, magnesium hydroxide carbonate, after a test dose of 450 mg. The same reference product was used in the present study. Using an identical test dose, *Jahnen* and *Hesse* (1990) [14] reported an elevated excretion of 0.87 mmol after ingestion of magensium oxide capsules and a level of 1.76 mmol after magnesium carbonate effervescent tablets.

In the present study magnesium excretion was not more pronounced even with a 33% higher test dose. This could have been due to non-linear saturation kinetics, which appeared to have already reached a maximum with a test dose of 450 mg.

The percentage of absorption in relation to test dose was therefore much lower (6.1% or 6.48%) in the present trial than the values of 10% and 8.5% obtained previously by *Schlebusch* et al. (1992) [28].

Surprisingly, the values for the second test day displayed a far greater variability, which was independent of the substance ingested. This is clearly reflected in the scatter of the readings obtained for magnesium excretion on that test day: For Group 1, the variation coefficient was increased by 60% (from 15.5% to 24.7%), while for Group 2 it more than doubled (from 13.7% to 27.7%).

Although magnesium elimination was increased in both groups, it was still only 1.24 mmol for Group 1 and 0.77 mmol for Group 2.

Hence variations in bioavailability, as calculated from this data, related more closely to the test day than to the form of magnesium supplement taken.

The picture becomes a little clearer and more consistent if the two days following the test days are also taken into account. Our own preliminary experiments showed that after saturation of the endogenous magnesium stores it takes at least 72 hours for excretion to reach a basal rate again, not 24 hours as was formerly supposed. Including the additional excretion on the two days following the test days into the calculation of bioavailability alters the results quite dramatically: For the first test day this yields values of 2.74 mmol and 2.44 mmol for Groups 1 and 2 respectively corresponding to percentage absorptions of 11.09% and 9.88%, while for the second test day bioavailability comes to 2.13 mmol and 2.60 mmol and percentage absorption to 8.62% and 10.53% for the two groups.

Even with this modified method of calculation, there were still no significant differences between the results obtained for the test and reference preparations.

Reviewing the literature one finds little agreement between the results of the various studies of magnesium excretion after single or multiple doses of a magnesium test product. This could, however, stem from fundamental differences in experimental design, variations in the composition and form of administration of the magnesium sup-

plement or the different doses used [8, 10–12, 16–18, 21, 22, 27, 32, 33, 35].

A precondition of a cross-over trial is that the two test days be independent of each other. Normally this is guaranteed by inclusion of an intermediate wash-out stage of 4 days, but the present study suggests that this is insufficient:

1. After a test dose of 600 mg magnesium (and in the preliminary trials after a dose of 350 mg) magnesium excretion took three days to stabilise and had by no means reached the former level in 24 hours. Investigations of magnesium bioavailability that limit measurements of excretion to the test day itself will therefore yield falsely low results.

2. Although the basal level of excretion was reached after three days, a second dose of the test product six days later appears to have been assimilated and processed differently by the body than that ingested on the first tast day. This is reflected in the greater scatter of results and in the significantly lower level of excretion on the second test day.

It indicates that for estimations of bioavailability in a cross-over trial such as this, the interval between the two test days needs to be widened; the optimal time interval cannot, however, be established from the results of this study.

Contrary to expectations, relating the results to individual fluctuations in creatinine elimination in each test person increased the scatter of the magnesium excretion values [2, 6, 9, 13, 24, 25, 29]. In other words, the scatter of the magnesium/creatinine quotients on the test days was higher than the scatter of the uncorrected magnesium elimination values.

Although plasma levels of magnesium are subject to an effective homeostasis, intake of a single dose of 600 mg magnesium temporarily overloads the body's regulatory capacity. Figure 3 illustrates how magnesium levels rose steadily after administration of the test dose, peak levels being reached within 2 hours in both groups and on both test days. The mean increase above the original level was 0.05 mmol/l. This finding contradicts the results of the author's previous study (*Schlebusch* et al. (1992) [28]) in which no change was observed in plasma levels; although it should be added that for those experiments a lower test dose of only 450 mg magnesium was used.

Whether this discrepancy was caused solely by the different dosages used cannot be definitively established owing to some differences in experimental design and conditions.

In their previous paper published in 1992, *Schlebusch* et al. [28] discuss the possible effect of erythrocyte stores on magnesium homeostasis. In that study, however, only 3 volunteers were tested. The present results obtained from 16 volunteers on two test days provide clear evidence that ingestion of magnesium supplements does not affect magnesium content of the erythrocytes.

Changes in calcium levels mirror the timecourse of fluctuations in magnesium, significant increases in excretion rate being observed on both test days, and a basal rate being re-established only 72 hours after administration of the test dose of magnesium.

Here too, the results obtained for the two test days appear not to be fully independent of each other.

Plasma levels of calcium are also affected by the absorption of magnesium, due to a proven interaction between the parathyroid hormone and magnesium [15, 20, 30, 31, 34]:

Increased plasma levels of magnesium, resulting from a massive dose of supplementary magnesium cause a reduction in parathormone secretion. This in turn lowers the tubular reabsorption of magnesium thereby raising the rate of excretion. The same applies to calcium excretion [7].

Plasma calcium concentrations peak after 2 hours, but on the whole the changes observed are less marked than the effects on magnesium.

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