Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study

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In order to evaluate the prophylactic effect of oral magnesium, 81 patients aged 18–65 years with migraine according to the International Headache Society (IHS) criteria (mean attack frequency 3.6 per month) were examined. After a prospective baseline period of 4 weeks they received oral 600 mg (24 mmol) magnesium (trimagnesium dicitrate) daily for 12 weeks or placebo. In weeks 9–12 the attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group compared to the baseline ($p < 0.05$). The number of days with migraine and the drug consumption for symptomatic treatment per patient also decreased significantly in the magnesium group. Duration and intensity of the attacks and the drug consumption per attack also tended to decrease compared to placebo but failed to be significant. Adverse events were diarrhea (18.6%) and gastric irritation (4.7%). High-dose oral magnesium appears to be effective in migraine prophylaxis. □ *Magnesium, migraine, NMDA-receptor, prophylaxis*

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A possible link between magnesium deficiency and migraine has been suggested recently (1). Low magnesium levels were demonstrated in the blood, blood cells and saliva of migraineurs (2–8), even though not all results were uniform (9). Reduced intracellular concentration of magnesium in the cortex of migraine subjects was shown, using ^{31}P-magnetic resonance spectroscopy (^{31}P-MRS) (10). Cerebrospinal fluid levels of magnesium are significantly low in migraine, both ictally and interictally (11). Furthermore, magnesium deficiency can lead to many physiological changes, some of which may be important in migraine pathophysiology (12–14). *In vitro* animal and human studies have shown that low magnesium (a) induces cerebral arterial vasospasm (15); (b) potentiates the contractile response of blood vessels to vasoactive substances such as serotonin (16, 17); (c) enhances the sensitivity of NMDA receptors to glutamate (18), thus inducing epileptiform discharges and cortical spreading depression (19, 20); (d) increases platelet aggregation leading to serotonin release (21); and (e) may be pro-inflammatory (22).

In view of the above, therapeutic trials with magnesium for migraine seem to be justified. In 1933 (23) a case of successful migraine prophylaxis was reported after injections of magnesium sulfate. Since that time no controlled study on magnesium therapy in migraine has been published except for a small sample of 20 patients with menstrual migraine (2).

Patients

The study was conducted at eight outpatient general or neurological practice centers. Patients, 18–65 years old, who met IHS criteria for migraine with or without aura (24) were eligible. All patients underwent routine physical examinations, and blood was obtained for the determination of potassium, calcium, creatinine, and serum magnesium (atomic absorption spectrophotometry) concentrations. When appropriate, levels of hemoglobin, hematocrit, total protein, cholesterol, triglycerides, high-density lipoprotein (HDL), and counts of red and white blood cells were determined. Exclusion criteria were pregnancy or nursing, known ammonium-phosphate-calculus-diatheses, kidney function disorders with serum-creatinine higher than 1.5 mg/dl, other interfering medical disorders, known allergies to any component(s) of the preparations, serious psychiatric diseases, tendencies towards substance-dependent or abusive behavior, and inability to distinguish migraine from other headaches.

The inclusionary and exclusionary criteria were established retrospectively and checked by the prospective baseline phase. No patient took acute headache medication for more than 10 days per month. Two patients (one verum, one placebo) received beta-blockers (25 mg/day atenolol or 200 mg celiprolol) for arterial hypertension, two other patients (both placebo) received antidepressants (90 mg amitriptylin-*N*-oxide or 20 mg amitriptyline) for depres-

sion. The trial medication showed positive results in all four patients. Furthermore, the patients had not taken any psychoactive drugs or migraine prophylactics in the 3 months prior to the beginning of the study. Acetylsalicylic acid (used by 23.5% of the patients), sumatriptan (18.5%) and metoclopramide (12.4%) were the most frequently used monopreparations for the acute therapy of migraine attacks during the baseline period. The most frequently used mixed preparations were ergotamine tartrate and caffeine (43.2%) or simple analgesics or non-steroidal anti-inflammatory drugs (NSAID) and codeine (18.5%). The patients took on average 2.52 acute medication single doses per attack during the baseline phase. The calculation of single doses for monopreparations was done, with the permission of, and according to, Diener (25). When combination preparations with several components were used (mostly NSAID and codeine or ergotamine tartrate and caffeine), a tablet or suppository was established as a single dose, since the dosage of the main ingredients corresponded to the pre-established single doses. In order to include the various potencies of the preparations and the patients' "drug-transfers" the preparations were given weight in four groups. Preparations from groups 1 and 3 were used most frequently (Table 1).

The study was conducted in accordance with the European Guidelines for Good Clinical Practice. Ethics committee approvals were obtained and written informed consent was given by each patient following a full explanation of the study and the required procedures prior to entry.

Trial design

The study lasted a total of 16 weeks for each patient. Following a 4-week baseline period (weeks −4 to 0) and a double-check of the inclusionary criteria, the patients were double-blind and randomly assigned to magnesium or placebo in blocks of four patients. The verum group received 600 mg (24 mmol) magnesium (trimagnesium dicitrate, Magnesium Diasporal® N 300, Protina GmbH, Germany) in the form of a water soluble granular powder every morning, the others received a magnesium-free placebo-powder for 12 weeks.

Table 1. Weighting of the drugs used for symptomatic treatment.

Factor	% of patients	Preparations
1	46.9	Antiemetics, NSAID, simple analgesics, caffeine, antihistamines, and combinations of the latter
2	28.4	Combinations of factor 1 drugs with codeine, dihydroergotamine preparations
3	64.2	Ergotamine preparations, sumatriptan p.o., other opioids
4	7.4	NSAID or antiemetics i.v., ergotamine s.c., i.m., sumatriptan s.c.

p.o., *per os*; i.v., intravenous; s.c., subcutaneous; i.m., intramuscular.

Patients kept a headache diary during the entire study period, and recorded the number, intensity and duration of the attacks as well as the dose of the acute medication(s) and any adverse events. Data from the diaries were checked and recorded at the test center every 4 weeks. The patients were asked if the study medication was taken as prescribed and if the headaches experienced were in fact migraine attacks. The duration of the attacks was recorded in days and the average intensity of the attacks was recorded using a visual analog scale (0=no pain, 10=the most intense pain). The re-occurrence of a migraine within 24 h, which had been initially and successfully treated, or had been interrupted by sleep, or was spontaneously remittent was classified as belonging to the initial attack. The patients were instructed to continue their usual acute treatment of migraine attacks and to return unused study medication to the test centers.

Evaluation of results

In accordance with IHS guidelines (26), reduction of the attack frequency in weeks 9–12 compared to the baseline rate was established as our main efficacy parameter. Secondary efficacy parameters were (1) reduction of the number of days with migraine; (2) duration of attacks in days; (3) intensity of the attacks on the pain scale; and (4) drug consumption per 4-week observation cycle. The number of administered single doses per patient and per patient per attack was determined and intraindividually compared for analysis.

The evaluation was done according to the intention-to-treat principle. It includes all patients who submitted an at least 4-week long headache diary and who randomly received the study medication. The last available findings were extrapolated (last value-carried-forward principle) until the end of the study for those patients who dropped out in the course of the study.

A protocol-correct analysis for the efficacy parameters was simultaneously carried out. The protocol-correct collective comprised 68 patients (36 verum, 32 placebo). Various responder analyses were carried out on the protocol correct collective. Here, patients who had a more than 50% reduction in attack frequency in weeks 9–12 compared to the baseline, whose attack reduction amounted to 50% or more as well as those whose attack frequency was below the baseline in weeks 5–8 and 9–12 were observed.

Statistics

Differences in the frequency of attacks, number of days with migraine, intensity, duration of migraine attacks as well as in the acute medication used between the two therapy groups were tested with the Wilcoxon–Mann–Whitney *U* test. Fisher's two-tailed exact test was used to compare the responders in the protocol-correct collective. Pearson correlation coefficient was determined for the initial magnesium serum levels and the reduction of attack frequency. Values of less p than 0.05 were considered significant. Center effects were excluded following a bifactoral variance analysis. The statistical evaluation was done using a SAS® system (version 6.10).

Results

A total of 81 patients were recruited; 43 in the magnesium group and 38 in the placebo group. The demographics and headache characteristics of both groups are shown in Table 2. Sixty-eight patients (84%, 36 verum, 32 placebo) finished the study according to plan. Eight patients dropped out; one (placebo) because of a lack of effectiveness, three others (verum) due to unwanted side effects and four (three placebo, one verum) were lost to follow up. Two patients (placebo) began using unauthorized medications (one metoprolol, one pizotifen), three others (verum) interrupted the intake or reduced the dosage due to unwanted side effects.

In all, 17 adverse events in 15 patients were documented. Five events were unrelated to the medication. Two patients in the placebo group reported moderate diarrhea. Eight patients (18.6%) in the verum group reported either diarrhea or soft stool within the first 4 weeks of therapy. This led two patients to drop out and two others to either reduce the dosage or interrupt therapy. All other patients continued the treatment as planned. Two patients (4.7%) in the verum group complained of gastric irritation, which led one patient to drop out and in the other case, accompanied by diarrhea, to an interruption of therapy. These symptoms were also completely reversible without further therapy.

Table 2. Patient baseline characteristics; means ± SD.

	Magnesium ($n=43$)	Placebo ($n=38$)
Sex (F/M)	37/6	33/5
Age at entry (years)	43.8 ± 10.7	47.6 ± 10.0
Duration since onset (months)	203.2 ± 130.8	181.6 ± 125.5
Frequency of attacks/4 weeks	3.63 ± 1.76	3.66 ± 1.71
No. of days with migraine/4 weeks	4.95 ± 2.69	5.47 ± 3.19
Duration of attacks (days)	1.42 ± 0.76	1.66 ± 1.22
Severity of attacks (VAS)	6.02 ± 1.87	6.35 ± 1.92
Serum magnesium level (mmol/l)	0.82 ± 0.10	0.86 ± 0.08

VAS, visual analogue scale.

Efficacy parameters

The development of the main and secondary efficacy parameters is shown in Figs. 1–4 and in Table 3. On average, the frequency of attacks was significantly reduced in the magnesium group [1.51 (41.6%)] compared to the placebo treated patients [0.58 (15.8%)] ($p=0.0303$). In the protocol-correct analysis, the difference was even more pronounced ($p=0.0275$). This treatment-effect already appeared in weeks 5–8 compared to the baseline ($p=0.0443$). The reduction of the number of migraine days was also significantly reduced in the magnesium patients [2.49 (52.3%)] compared to the placebo group [1.16 (19.5%)] ($p=0.0344$). The protocol-correct collective analysis showed that the difference was not statistically significant ($p=0.0854$).

The reduction of the average duration of attacks in days as well as that of the average pain intensity were more noticeable in the verum group than in the placebo group, but the differences were not statistically significant. The per person consumption of acute medication in the verum group declined

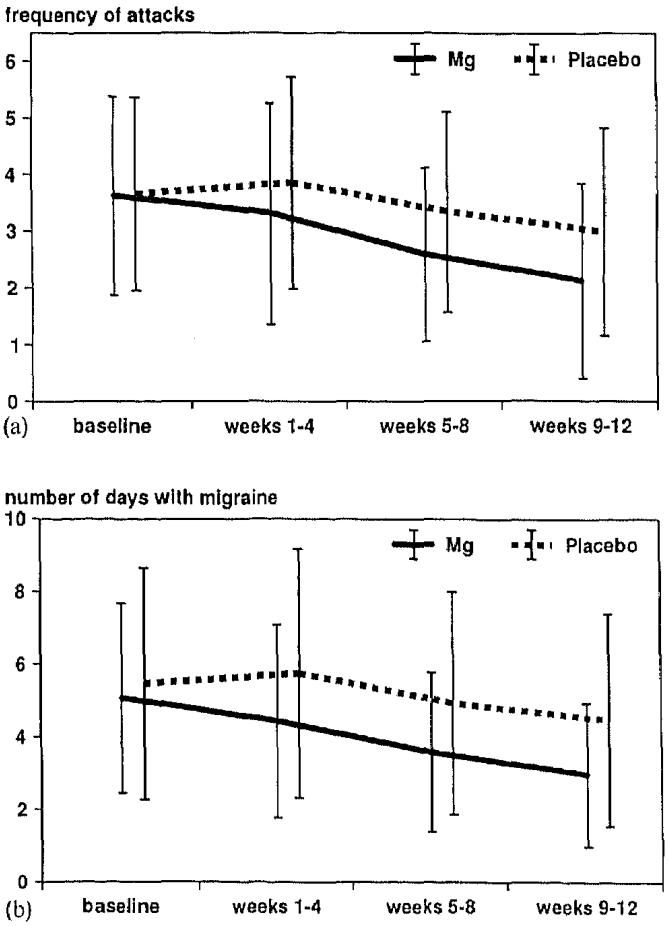

Fig. 1. Attack frequency (upper panel) and migraine days (lower panel). Magnesium was significantly superior to placebo in reducing attack frequency at weeks 5–8 and 9–12 compared to the baseline phase ($p<0.05$). Magnesium was superior to placebo in reducing migraine days at weeks 9–12 compared to baseline ($p<0.05$).

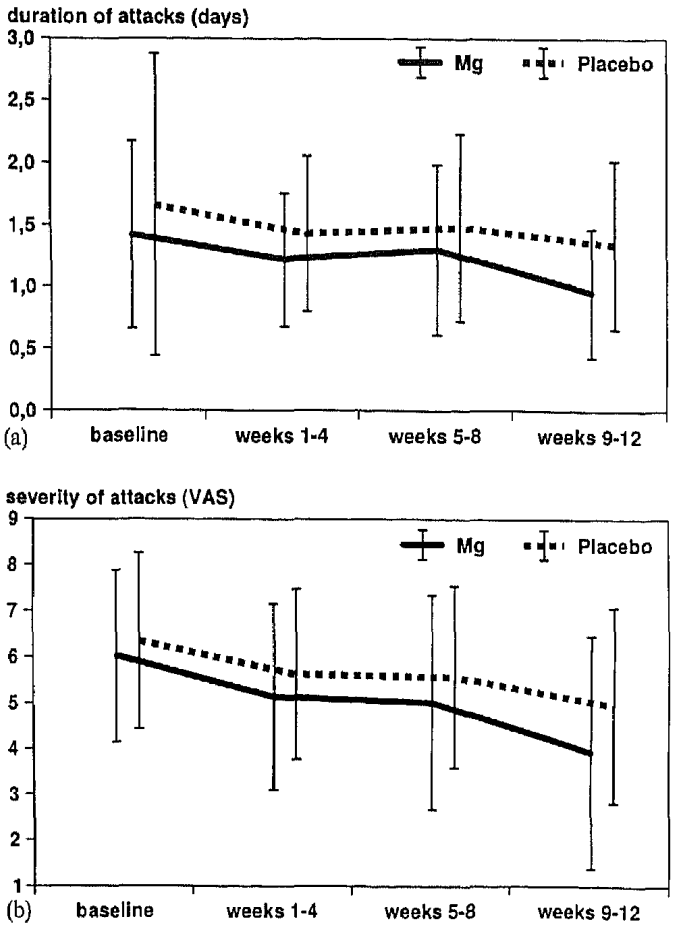

Fig. 2. Duration (above) and intensity (below) of attacks. Magnesium was not superior to placebo; VAS, visual analogue scale.

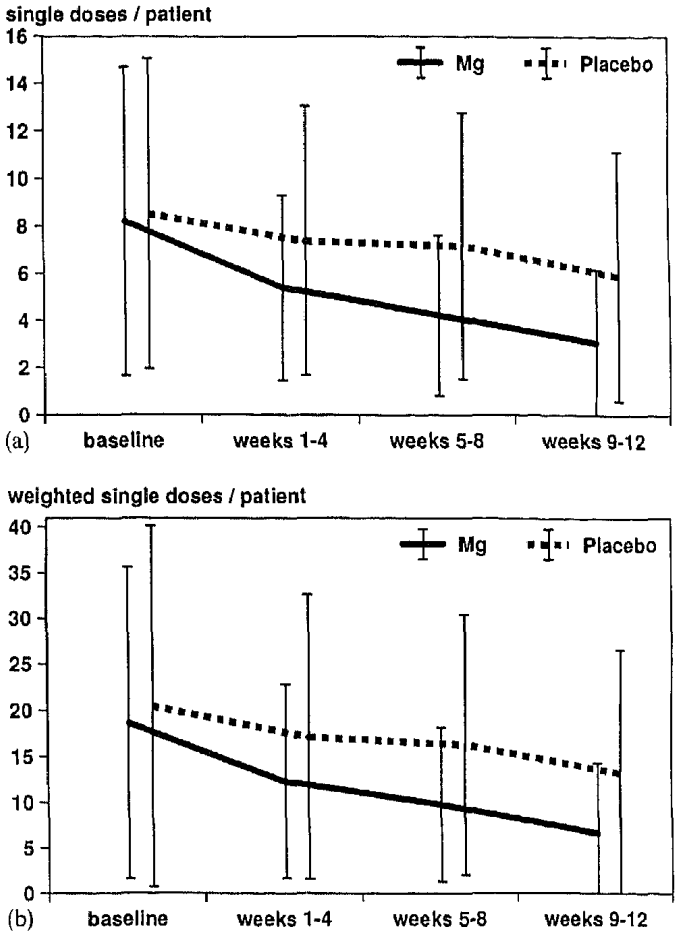

Fig. 3. Consumption of acute medication per patient. Magnesium was superior to placebo in weeks 5–8 and 9–12 compared to the baseline phase ($p<0.05$); for weighting see Table 1.

Table 3. Efficacy parameters; mean reduction ± SD, 95% confidence intervals are given in parentheses.

	Magnesium ($n=43$)	Placebo ($n=38$)	p value
Frequency of attacks	1.51 ± 2.07 (0.87–2.15)	0.58 ± 2.30 (−0.18–1.33)	0.0303
No. of days with migraine	2.49 ± 3.05 (1.55–3.43)	1.16 ± 3.89 (−0.12–2.44)	0.0410
Duration of attacks (days)	0.48 ± 0.80 (0.23–0.73)	0.27 ± 1.35 (−0.18–0.71)	0.2134
Severity of attacks (VAS)	2.06 ± 2.77 (1.21–2.91)	1.25 ± 2.29 (0.50–2.00)	0.3199
Drug consumption (single doses)			
p. pt. (unweighted)	5.07 ± 6.58 (3.05–7.10)	2.40 ± 6.59 (0.23–4.57)	0.0159
p. pt. (weighted)	12.03 ± 16.69 (6.90–17.17)	6.73 ± 18.33 (0.71–12.76)	0.0252
p. pt. per attack (unweighted)	1.13 ± 1.75 (0.59–1.66)	0.53 ± 2.56 (−0.31–1.37)	0.1514
p. pt. per attack (weighted)	2.42 ± 3.24 (1.42–3.42)	1.75 ± 7.32 (−0.66–4.15)	0.2096

*Wilcoxon 2-sample test; weeks 9–12 compared to baseline.
VAS, visual analogue scale.

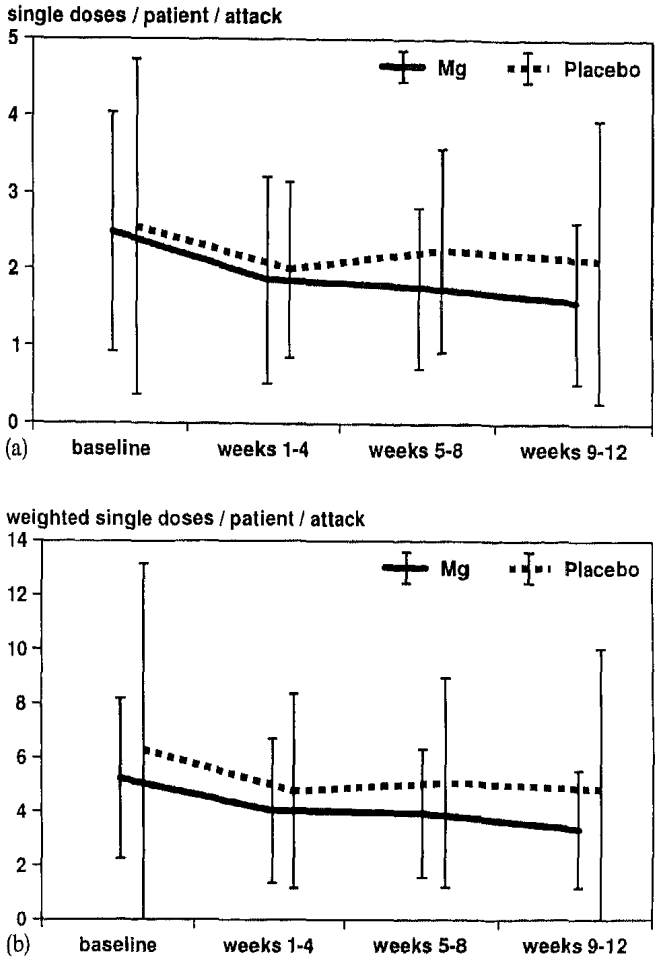

Fig. 4. Consumption of acute medication per patient per attack. Magnesium was not superior to placebo; for weighting see Table 1.

correspondingly with the decline in attack frequency and the number of migraine days and thus indirectly confirmed the success of the therapy. This was also true for the weighted single doses, so that a success of shorter attacks by means of a drug-transfer to more potent preparations can be ruled out. Magnesium also was superior to placebo both in the weighted and unweighted calculation in weeks 5–8 compared to the baseline ($p=0.0394$ and $p=0.0360$, respectively). The individual dosage per attack as indirect evidence of duration and intensity also showed a greater decline in the verum group than in the placebo group, but the difference was not statistically significant.

In the last 4-week period, 52% of the verum patients had at least a 50% reduction in the number of attacks in comparison to the baseline rate. The number of responders in the verum group was higher than the number in the placebo group in all three calculations but the differences did not reach statistical significance (Table 4).

The correlation (Pearson correlation coefficient) between the initial magnesium serum levels and the reduction of attack frequency was 0.07 ($p=0.5301$).

Discussion

We have demonstrated that a high oral dose of magnesium lowered the frequency of migraine attacks within 12 weeks of therapy. Compared to placebo the therapeutic effect was already significant by the second therapy phase (weeks 5–8) and was confirmed by a significant reduction in the number of migraine days as well as the per patient consumption of acute medication. The duration and intensity of the attacks also declined without having reached the significance level in comparison to the placebo group. The largely identical results with weighted and unweighted medication records rule out the possibility that patients resorted to stronger or weaker preparations in the course of the study. The reporting of attack duration in days is, in any case, rather inexact, so that a significant reduction possibly could not be recorded. The fact that attack frequency, number of days with migraine and drug consumption for acute treatment significantly decreased but parameters of the single attacks (intensity, duration, drug consumption) did not, would suggest an "all-or-none principle" of migraine prophylaxis with magnesium. A single attack could be prevented, but when it occurs its duration and intensity remain relatively unchanged.

The results confirmed the positive effect of 300 mg magnesium in a small, select sample of 20 female patients with menstrual migraine. In that study, however, in addition to the number of headache days, the duration and intensity of the attacks, as recorded by means of a total pain index, also declined significantly (2).

The reduction of attack frequency is the main efficacy parameter according to the IHS guidelines (26). We observed a 25.8% advantage of high-dose oral magnesium therapy over the placebo group. In comparison, a meta-analysis of all studies using propranolol showed a somewhat greater advantage

Table 4. Evaluation of responders (protocol correct).

	Magnesium ($n=36$)	Placebo ($n=32$)	p value
>50% reduction in attack frequency (weeks 8–12 compared to baseline)	14 (38.9%)	7 (21.9%)	0.189
⩾50% reduction in attack frequency (weeks 8–12 compared to baseline)	19 (52.8%)	11 (34.4%)	0.149
Baseline attack frequency reduced from week 5 onward	20 (55.6%)	10 (31.3%)	0.054

*Fisher's exact test (two-tailed).

at 33.1% compared to placebo and 43.7% compared to the previous therapy (27). It is to note that the efficacy parameter used in the latter study was a headache index (duration × intensity) which is no longer recommended (26).

The side effects of high-dose oral magnesium included diarrhea and gastric complaints. These complaints were mild and tolerable. Only 7% of the verum patients discontinued therapy due to these problems, which seems minor in comparison to common migraine prophylactics and therefore favorable for patient compliance. It remains to be seen whether lower doses of magnesium could reduce the frequency of side effects and still prevent migraine, as suggested by some (2, 28). Interestingly, of the two verum patients who halved their doses due to unwanted side effects and therefore were excluded from the protocol-correct analysis after the end of the study, one was among the responders who reported a >50% reduction in attack frequency.

There was no significant correlation between the serum magnesium levels prior to therapy and the reduction of attack frequency. We have no information about serum level changes during treatment. It was demonstrated recently that both 12 and 24 mmol magnesium administered orally as trimagnesium tricitrate significantly elevated the magnesium plasma level within 12 h by 3.1 and 4.6%, respectively (29). A pharmacodynamic action of magnesium can thus be hypothesized. The anticonvulsant and antihypertensive effects of parenterally administered magnesium are well known from the prevention and treatment of eclampsia (30, 31). Its vasodilatory, anti-arrhythmic, antiplatelet and possibly ischaemia protective effects are supposed to improve the outcome of acute myocardial infarction (32) and ischemic stroke (33). Successful therapy of acute attacks of migraine and cluster headache by parenteral magnesium has been reported (34).

High-dose oral magnesium appears to be effective in migraine prophylaxis with a reasonable adverse events profile. The results of this study require further investigations with a greater number of patients. Whether certain patient subgroups, i.e. patients with menstrual migraine, subjects with tension-type headache and migraine or those with migraine with aura, can especially profit from a magnesium therapy should be examined in responder analyses.

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