Magnesium Treatment of Primary Alcohol-Dependent Patients During Subacute Withdrawal: An Open Pilot Study With Polysomnography

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Background: Sleep electroencephalogram alterations and insomnia complaints persist after alcohol withdrawal in dependent patients and are considered strong predictors of relapse. Although disturbances of magnesium household due to alcohol consumption are well known, the relationship of magnesium metabolism and sleep disturbances has not been investigated in this patient group. We conducted an open pilot study to evaluate the effects of magnesium treatment on the sleep of primary alcohol-dependent patients during subacute withdrawal.

Methods: Patients were treated with 30 mmol magnesium daily over 4 weeks. Eleven of the 14 included patients were evaluated. Patients were free of any kind of psychotropic medication or other substances known to influence sleep. Polysomnographic recordings with monitoring of periodic leg movements in sleep (PLMS) were performed for two consecutive nights 2 weeks after acute withdrawal (baseline) and 4 weeks later at the end of the treatment period. After the baseline polysomnography, patients were investigated by the magnesium loading test to verify magnesium depletion.

Results: We found a significant decrease of sleep onset latency from 40.6 to 21.7 min ($p = 0.03$) and a significant improvement of subjective sleep quality, as assessed by the Pittsburgh Sleep Quality Index, from 8.1 to 5.8 ($p = 0.05$) during magnesium treatment. Changes in PLMS indices revealed two subgroups of patients: one with an increase of PLMS from 30.7 to 39.4 per hour of sleep ($n = 4$) and the other one with a decrease of PLMS from 8.9 to 2.1 per hour of sleep ($p = 0.04$). Patients with PLMS decreases seemed to have a more favorable prognosis: total sleep time, γ-glutamyltransferase, carbohydrate-deficient transferrin, and Beck Depression Inventory scores improved significantly during treatment in this group. The magnesium loading test revealed a magnesium deficiency in only one patient, five patients showed normal retention values, and the remaining five patients had an increased magnesium excretion, indicating a possible continued renal magnesium loss during abstinence.

Conclusions: The results of this study should be interpreted with caution, because no control group with placebo was investigated. Both subjective and, partly, objective parameters of sleep improved during the 4-week study period. Further research is needed to clarify the relationship of magnesium metabolism and sleep alterations.

Key Words: Alcohol Withdrawal, Sleep, Magnesium, Periodic Leg Movements in Sleep, Treatment.

SLEEP DISTURBANCES ARE among the most frequent complaints from alcohol-dependent patients during periods of drinking, as well as during withdrawal or abstinence. Recovered patients may show persistent sleep abnormalities for months or even years (Gillin and Drummond, 2000).

Sleep electroencephalogram (EEG) investigations have demonstrated fragmented sleep during acute alcohol withdrawal and alterations of sleep architecture with reduced sleep time, frequent sleep stage shifts, reduction or loss of slow-wave sleep, and significantly increased sleep onset latency during the first months of abstinence (Benca et al., 1992; Foster and Peters, 1999; Snyder and Karacan, 1985; Williams and Rundell, 1981). Reports on rapid eye movement (REM) sleep changes have yielded inconsistent findings. Persistent REM sleep abnormalities were evident in depressed alcohol-dependent patients (Gillin et al. 1990a) and in those who subsequently relapsed (Brower et al., 1998; Gann et al., 2001; Gillin et al., 1994). Spectral EEG analyses of abstaining primary alcohol-dependent patients have shown lower delta activity, reductions in mean spectral power, and decreases of delta and theta activity during the first period of non-REM sleep (Irwin et al., 2000; Feige et al., unpublished data, 2004). The number of periodic leg movements in sleep (PLMS) was found to be increased during alcohol abuse in some but not in all subjects (Aldrich and Shipley, 1993; Gann et al., 2002; Le Bon et al.,

1997). An increased PLMS index (number of PLMS per hour of sleep) was associated with relapse during a 6-month observation period in a longitudinal study (Gann et al., 2002). Sleep EEG alterations and insomnia complaints persist up to 24 months after alcohol withdrawal and are considered a strong predictor of a relapse (Brower et al., 1998, 2001; Drummond et al., 1998; Foster and Peters, 1999; Gillin et al., 1994). Therefore, factors that contribute to sleep abnormalities in alcoholism have attracted increased attention during recent years.

Although disturbances of magnesium homeostasis and low serum magnesium levels in alcohol-dependent patients have been reported previously (De Marchi et al., 1993; Elisaf et al., 1995; Flink, 1986; Glue and Nutt, 1990), the relationship between magnesium metabolism and sleep disturbances has not yet been investigated in this disorder. Possible pathophysiological mechanisms of magnesium depletion during chronic alcohol consumption include a renal magnesium loss or a reduced magnesium intake due to an unbalanced diet. Renal magnesium loss during alcohol consumption may emerge due to increased renal tubular magnesium excretion, reduced antidiuretic hormone levels, or low parathormone secretion (Abbott et al., 1994; Rylander et al., 2001). Prolonged renal tubular dysfunction leading to magnesium loss could be shown even after 4 weeks of abstinence (De Marchi et al., 1993). In animals, magnesium deficiency is accompanied by sleep disturbances (Depoortere et al., 1993; Poenaru et al., 1984), whereas higher magnesium contents in specific brain areas correlate with longer slow-wave sleep episodes during recovery after sleep deprivation in mice (Chollet et al., 2000). In humans, magnesium treatment increased slow-wave sleep in healthy elderly subjects (Held et al., 2002) and resulted in an improvement of sleep efficiency and in a reduction of PLMS in patients with PLMS-related insomnia or restless legs syndrome (Hornyak et al., 1998).

In view of the findings reported previously, we conducted an open pilot study to evaluate the effects of magnesium treatment on the sleep of primary alcohol-dependent patients during subacute withdrawal. Our hypothesis assumed a normalization of sleep parameters during magnesium treatment and a reduction of PLMS after the 4-week treatment period.

METHODS

Subjects

Fourteen patients were initially intended to participate in the study. Because 3 patients dropped out during the study (for various reasons; see below), 11 patients remained for the final data analysis. Patients fulfilled DSM-III-R criteria for alcohol dependence (Structured Clinical Interview for DSM-IV, German version; Wittchen et al., 1988). None of the patients was diagnosed with a (preexisting) comorbid psychiatric disorder such as major depression; i.e., all patients had primary alcohol dependence (Schuckit, 1985). Patients with cognitive impairment, major medical problems, intercurrent infections, sleep apnea syndrome, treatment with anti-craving substances, regular magnesium intake the 2 weeks before the study, renal failure (risk of magnesium accumulation), or heart failure

(contraindication to parenteral magnesium treatment) were excluded from the study. All patients were free of any kind of psychoactive medication for a minimum of 7 days before the first polysomnographic investigation and during the study. Patients with prolonged alcohol withdrawal syndrome requiring ongoing psychotropic medication or the use of antihypertensive drugs influencing sleep (such as clonidine) during the week before polysomnography were not included (i.e., any sort of treatment to relieve withdrawal symptoms during the second week of withdrawal was an exclusion criterion). The only medication allowed during the week before polysomnography was nifedipine for the treatment of increased blood pressure values. One patient with hypertension had already been treated with metoprolol before the withdrawal, whereas none of the other patients was receiving a continuous comedication possibly influencing electrolyte metabolism or interacting with the action of magnesium. Patients with depressive symptoms were also excluded [the depressivity score of the included patients was 9.6 ± 7.0 on the Beck Depression Inventory (BDI); see below]. Three patients dropped out of the study: one patient was diagnosed with an additional depressive disorder 3 days after being included in the study, one patient had taken codeine-containing medicine because of an intercurrent bronchitis, and one patient did not show up for the polysomnographic investigation at the end of the study. The study was approved by the local ethics committee, and each patient signed written informed consent before inclusion.

Five of the 11 patients included in the evaluation were male (aged 48.2 ± 8.9 years, mean $\pm$ SD), and 6 were female (aged 45.8 ± 7.3 years). The daily alcohol consumption before withdrawal was 349 ± 102 g in male and 196 ± 76 g in female patients (265 ± 116 g for the group as a whole). On average, the duration of alcohol dependence was 16.8 ± 9.7 years, and patients had a history of 2.2 ± 1.9 withdrawals. Carbohydrate-deficient transferrin (CDT), determined at the beginning of the treatment period, was slightly reduced at the end of the study (17.6 ± 5.9 units/liter and 15.2 ± 6.8 units/liter, respectively; $p = 0.02$). γ-Glutamyltransferase (GGT) decreased in all patients during treatment, indicating abstinence (GGT at admission to the hospital was 115 ± 156 units/liter and at the end of the study 6 weeks later was 22 ± 27 units/liter; $p = 0.003$). All patients showed normal serum magnesium levels before treatment (0.864 ± 0.082 mmol/liter), with an increase at the end of treatment (0.905 ± 0.082 mmol/liter).

Procedures

Patients had been admitted for alcohol withdrawal and treatment of alcoholism to our department, which offers a 21-day inpatient treatment program. All subjects underwent a full medical and psychiatric examination, as well as various laboratory tests (routine clinical hematological laboratory examination, urine analysis, electrocardiogram, and EEG). An additional urine analysis was performed to detect the use of benzodiazepines, opioids, cannabinoids, amphetamines, and cocaine before polysomnographic investigations. Only patients with negative results were included. One patient with positive codeine screening at the end of the study was excluded from the evaluation (described previously). Patients were investigated for exclusion criteria 1 week after the beginning of acute alcohol withdrawal and were invited to participate in the study. Polysomnographic investigations were performed 2 weeks (16.2 ± 3.7 days) and 6 weeks (47.2 ± 4.3 days) after the beginning of abstinence (Fig. 1). Patients were discharged from the hospital 3 weeks after admission (i.e., approximately 1 week after the beginning of the treatment period) and were contacted 10 days (± 2 days) later in the outpatient clinic to explore side effects of the medication. Breath alcohol tests were performed regularly during the stay in the department and at the time of outpatient contacts, including the polysomnographic investigation at the end of the study. Furthermore, serum levels of hepatic enzymes (GGT, alanine aminotransferase, and aspartate aminotransferase) and of CDT were determined at the end of the treatment period.

Magnesium Treatment

Patients were given 30 mmol of magnesium (magnesium-L-aspartate hydrochloride) per day: 10 mmol in the morning and 20 mmol in the
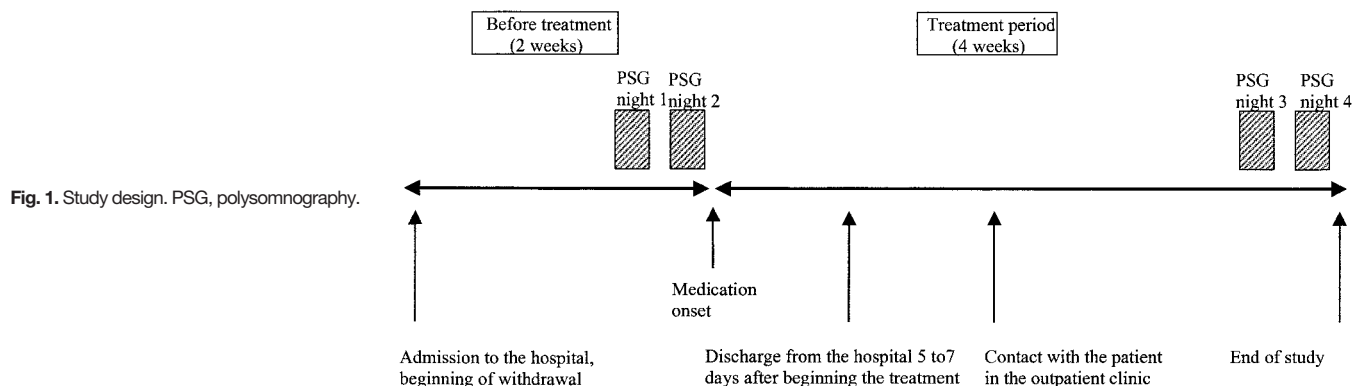
Fig. 1. Study design. PSG, polysomnography.

Polysomnography

Polysomnographic assessments included EEG (C3-A2, C4-A1), electro-oculogram, submental electromyogram, electrocardiogram, and superficial electromyogram of both anterior tibial muscles. In all patients, oronasal air flow, thoracic and abdominal breathing efforts, and transcutaneous oximetry were monitored during the first night of the study. Polysomnography recordings were performed from 11:00 PM (lights out) until 7:00 AM (lights on). Sleep recordings were visually analyzed by experienced raters according to the criteria of Rechtschaffen and Kales (1968). Arousals were scored as recommended by the American Sleep Disorders Association ("EEG arousals," 1992). PLMS were scored according to standard criteria ("Recording and scoring leg movements," 1993), i.e., only if they were part of a series of four or more consecutive movements lasting at least 0.5 sec, with an intermovement interval of 4 to 90 sec. PLMS were scored as associated with arousal if the arousal followed the beginning of the leg movement with an interval no longer than 3 sec. Total sleep time (TST) was calculated as the time spent in any sleep stage during the recording. Sleep efficiency was determined as the quotient of TST and the time in bed. The arousal index was defined as the number of arousals per hour of TST. Sleep onset latency was calculated as the time period between the beginning of the recording (lights out) and the first epoch of sleep stage 2, whereas REM sleep latency was determined as the interval between the first epoch of a sleep stage (but not of sleep stage 1) and the first epoch of REM sleep. REM density was defined as (number of REMs/number of REM epochs) $\times$ 100. The following indices were calculated regarding the frequency of PLMS: (1) PLMS index, indicating the number of PLMS per hour of TST; and (2) PLMAI (PLMS arousal index), measuring only the PLMS associated with arousals per hour of TST.

Self-Rating Scales

The Pittsburgh Sleep Quality Index (PSQI) was used to judge overall sleep quality in the 2 weeks preceding polysomnography (Backhaus et al., 2002; Buysse, 1989; German version in Riemann and Backhaus, 1996). The sum score of the PSQI ranges from 0, indicating no sleep disturbance at all, to 21, indicating a severe disturbance of sleep. The sum score is composed of seven components describing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. The BDI, a depression self-rating scale, was used to assess subjectively perceived depression

(Beck, 1978; German version, Hautzinger et al., 1994). The scale consists of 21 items. Scores less than 12 are regarded as normal, scores between 12 and 17 indicate mild depression, and scores greater than 18 signify a clinically relevant depression.

Magnesium Loading Test

Because serum magnesium level and tissue pools of magnesium are poorly correlated (except for the interstitial fluid) and because intracellular magnesium deficiency may exist despite normal serum magnesium levels (Elin, 1987), we used the magnesium loading test to verify magnesium depletion (Gullestad et al., 1994). We used the 1-hr version of the test (Rob et al., 1999) in our study because of its easier handling. Patients were given an intravenous magnesium load of 0.1 mmol of magnesium-L-aspartate hydrochloride per kilogram body weight on the morning after the second (baseline) polysomnography recording. Urine was collected over the next 24 hr to determine magnesium excretion. The amount of retention was calculated with the formula [1 − (24-hr urine magnesium content/magnesium test dose)] $\times$ 100, which gave a percentage value. The reference range for magnesium retention in healthy men and women is given at $6.3 \pm 10.3\%$, with the 0.025 and 0.975 fractiles at −19.5 and 27.5% (Gullestad et al., 1994).

Analyses

Comparisons of sleep EEG parameters were made with values from the second and fourth nights to exclude adaptation effects ("first night effect"; Mendels and Hawkins, 1967) in the sleep laboratory. Because the effect of magnesium in earlier studies was primarily at the beginning of the night (Held et al., 2002), the EEG data were additionally calculated for the first, second, third, and fourth parts of the sleep period time and also for the cumulative mean of these periods to reveal the dynamics of sleep changes. Comparisons of PLMS indices were made with mean values of both nights before and at the end of treatment (mean of nights 1 and 2 versus the mean of nights 3 and 4) because of the variability of PLMS previously described in several studies (Ancoli-Israel et al., 1991; Bliwise et al., 1988; Mosko et al., 1988). Statistical analyses were performed with Wilcoxon's signed rank test for paired comparisons because data were distributed nonparametrically. Correlations were calculated according to Spearman. Because the study was designed as an exploratory study for determining the effects of magnesium on sleep in this patient population and because the number of patients investigated in the study was small, we did not perform a correction for multiple comparisons in order not to miss clinically relevant effects of magnesium treatment. The level of significance (two tailed) was set at $p \leq 0.05$. All analyses were performed with the SPSS 9.0 statistical package (SPSS Inc., Chicago, IL).

evening. Magnesium-L-aspartate hydrochloride was chosen because its good absorption and tolerability (Muhlbauer et al., 1991; Weiss et al., 1986). Nonetheless, four patients developed slight diarrhea due to the magnesium-containing medication. These patients were instructed to take the daily dosage in three or four portions and to modify their diet by ingesting more food rich in pectins and/or foods known to reduce diarrhea (apples, rice, and so on). With these precautions, none of the patients had to reduce the magnesium medication.

Table 1. Polysomnographic Measurements of All Patients ($n = 11$) Before and at the End of Magnesium Treatment

	Before treatment	End of treatment	p Value
Sleep efficiency (%)	80.1 ± 8.1	82.5 ± 11.2	0.53
Total sleep time (min)	381 ± 37	403 ± 47	0.18
Number of stage shifts	182 ± 54	191 ± 48	0.37
Number of wake periods	32.7 ± 14.6	33.4 ± 14.0	0.90
Number of arousals	175 ± 77	192 ± 62	0.37
Sleep onset latency (to sleep stage 2)	40.6 ± 29.1	21.7 ± 14.5	0.03*
Sleep stage characteristics during sleep period time			
Awake (min)	48.0 ± 25.1	42.4 ± 22.1	0.42
Sleep stage 1 (min)	50.0 ± 17.3	48.1 ± 13.2	0.93
Sleep stage 2 (min)	232.0 ± 40.2	246.2 ± 29.8	0.29
Slow-wave sleep (min)	9.5 ± 13.7	11.9 ± 17.9	0.14
REM sleep (min)	91.5 ± 19.7	94.4 ± 33.6	0.66
REM sleep latency (min)	84.5 ± 41.5	78.9 ± 37.2	0.72
REM density	35.0 ± 12.3	31.6 ± 8.2	0.37
PLMS			
No. of PLMS per hour of sleep	15.6 ± 15.0	18.8 ± 26.7	0.57
No. of PLMS associated with arousal per hour of sleep	3.7 ± 3.9	4.9 ± 6.5	0.37

Values are given as mean ± SD.
* Statistical significance.
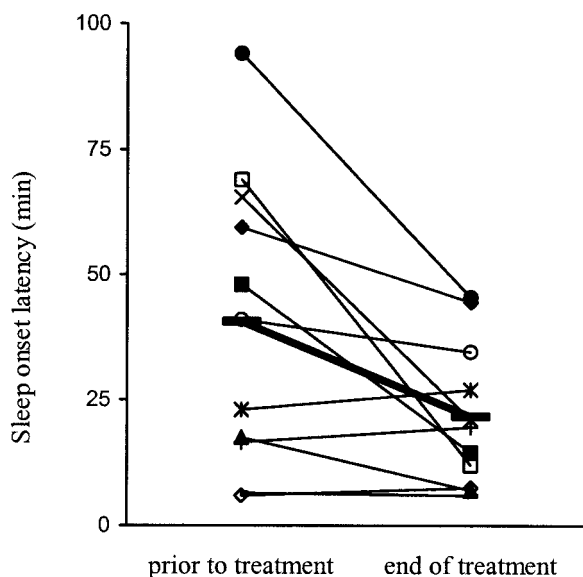
Fig. 2. Sleep onset latency (latency to sleep stage 2) in all patients before (night 2) and at the end of magnesium treatment (night 4). The solid line indicates mean values. The symbols for individual subjects are consistent across the figures.

RESULTS

Sleep EEG Parameters Before and at the End of the Magnesium Treatment Period

Sleep EEG parameters of all patients are shown in Table 1. Sleep latency decreased significantly at the end of the treatment period (Fig. 2). Sleep period time and slow-wave sleep increased slightly. Other polysomnographic parameters did not change during the course of magnesium treatment. The analysis of EEG data of the four periods of sleep period time also did not reveal any significant differences. Furthermore, we found no changes of REM sleep characteristics. Sleep EEG parameters correlated neither with alcohol consumption before withdrawal nor with the number of withdrawals, the duration of alcohol dependence, or the BDI score.

PLMS Before and at the End of the Magnesium Treatment Period

Changes in PLMS measures are shown in Table 1. PLMS index (number of PLMS per hour of sleep) and PLMAI (number of PLMS associated with arousal per hour of sleep) increased slightly until the end of treatment, although no consistent changes were detectable. Considering the individual values, two subgroups could be discerned, however (Fig. 3). Four patients showed an increase of PLMS indices at the end of treatment, and the other seven patients showed decreasing PLMS values.
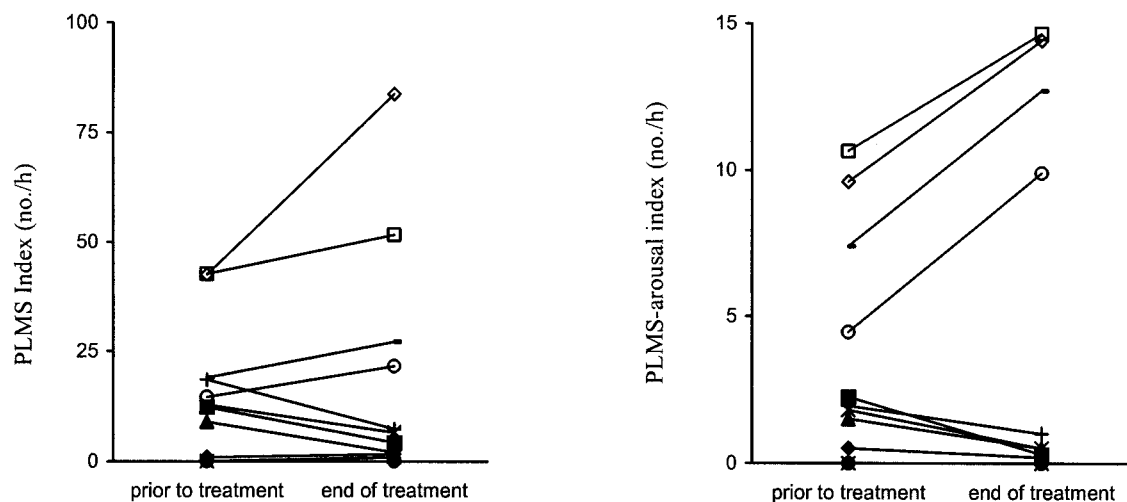
Comparison of PLMS Subgroups

Subgroups identified by the PLMS evaluation were analyzed separately (Table 2). Distribution of gender was similar in both groups (male/female: 2/2 vs. 3/4). Patients in the subgroups differed regarding laboratory and clinical characteristics. Patients with a PLMS increase during treatment had higher serum GGT and CDT levels before treatment, although their reported alcohol consumption before withdrawal was lower than in patients with a PLMS decrease. Patients with a PLMS increase also reported worse subjective sleep quality. Patients with a PLMS decrease seemed to have a more favorable prognosis, because TST, GGT, CDT, and BDI improved significantly during treatment in this group.

Subjective Sleep Quality and Self Rating of Depression Before and at the End of the Magnesium Treatment Period

Subjective sleep quality, as assessed by the PSQI, improved significantly during treatment from 8.1 ± 4.0 to 5.8 ± 2.7 ($p = 0.05$). Self-rated depression, as measured by the BDI, improved significantly from 9.6 ± 7.0 to 5.6 ± 4.0 ($p = 0.01$). Subjective sleep quality (PSQI) and depression scores (BDI) were not correlated ($r = -0.009$).

Results of the Magnesium Loading Test

One patient had an increased magnesium retention of 60%, which indicated magnesium deficiency. Five patients showed normal magnesium excretion with $-18 ± -14\%$. Another five patients had an increased magnesium excretion of $-74 ± -17\%$, which indicated potential renal magnesium loss. Patients in this group reported a higher daily alcohol consumption (322 ± 79.5 g versus 235 ± 134 g; $p = 0.09$). Polysomnographic and PLMS measures did not show any trend toward change, either in the normal or in the increased magnesium excretion group. The patient with magnesium deficiency did not display any relevant changes of polysomnographic measures during treatment. With regard to the PLMS subgroups, two patients with increased magnesium excretion belonged to the PLMS

Fig. 3. Values of the PLMS index and of the PLMS arousal index of all patients before (mean of night 1 and night 2) and at the end of magnesium treatment (mean of night 3 and of night 4).

Table 2. Description of PLMS Subgroups

	Patients with PLMS increase ($n = 4$)			Patients with PLMS decrease ($n = 7$)		
	Before treatment	End of treatment	p Value	Before treatment	End of treatment	p Value
No. of PLMS per hour of sleep	29.7 ± 15.0	46.0 ± 28.3	0.07	7.6 ± 7.4	3.2 ± 2.8	0.11
No. of PLMS associated with arousal per hour of sleep	8.0 ± 2.7	13.0 ± 2.2	0.07	1.1 ± 1.0	0.4 ± 0.4	0.04*
Total sleep time (min)	388 ± 46	366 ± 61	0.71	376 ± 32	423 ± 18	0.04*
Clinical and laboratory characteristics						
Age (years)		49 ± 9			46 ± 7	
Daily alcohol consumption before withdrawal (g)		223 ± 69			290 ± 135	
GGT at the beginning and end of acute withdrawal (units/liter)		144 ± 254 vs. 32 ± 46			99 ± 87 vs. 17 ± 9*	
CDT before and at the end of treatment (units/liter)		19.8 ± 7.5 vs. 18.3 ± 7.8			16.3 ± 5.0 vs. 13.4 ± 5.5*	
BDI before and at the end of treatment		8.3 ± 10.6 vs. 5.1 ± 6.1			10.4 ± 4.7 vs. 5.8 ± 2.8*	

Data are given as mean ± SD.
* $p < 0.05$.

increase group, and three patients belonged to the PLMS decrease group.

DISCUSSION

Our study is the first to investigate the effects of magnesium treatment on sleep in alcohol-dependent patients during subacute withdrawal. Because the study was designed as an open pilot study, no control group with placebo medication was included. Therefore, the results of the study should be interpreted with caution.

The main finding of the study was a significant reduction of sleep onset latency from 40.6 to 21.7 min during the treatment period. Williams and Rundell (1981) investigated the natural course of alcohol dependence and reported sleep onset latencies of 35 min after 35 days of abstinence in 46 men, with a slight improvement to 29 min, 2 months later. Drummond et al. (1998) found an improvement of sleep onset latency from 20 min after withdrawal to 16 min after a 5-month observation period. Gillin et al.

(1990b) described sleep abnormalities similar to the ones in our patients in 31 primary alcoholics aged 46 years during subacute withdrawal (8 to 32 days since the last drink). In their sample, sleep latency and TST were shorter (24 and 334 min, respectively) than in our study, perhaps because of the wider range of the studied abstinence interval. No follow-up of this group of patients was documented. Our study did not include a control group, which is the main limitation of the study, because an improvement of sleep onset latency has been described in the previously mentioned studies in untreated abstinent patients. However, the significant reduction of sleep onset latency found in our patients during treatment has not been reported in any previous naturalistic longitudinal studies; therefore, it could be attributed to treatment and not just to the process of sleep normalization during prolonged abstinence.

A further relevant finding of our study is the improvement of subjective sleep quality during the treatment period. The longitudinal study by Foster and Peters (1999) investigated the perceived sleep quality and described

PSQI scores remaining above normative levels (10.3 at baseline) over a 12-week observation period, even in subjects who did not relapse. This study has not been replicated up to now. It indicates, however, that subjective estimates of sleep disturbances do not always spontaneously improve and seem to remain fairly stable even over 3 months in abstaining patients. Insofar, our results might indicate an influence of magnesium treatment on the patients' subjective perception of sleep.

The analysis of PLMS data revealed two subgroups with different courses of PLMS changes. We cannot provide any conclusive interpretation for the subgroup differences. One explanation might be clandestine drinking in the PLMS increase group that led to worsening of PLMS parameters. However, even if patients had consumed alcohol in this subgroup, the amounts could have only been very small, because laboratory tests (CDT and GGT) and breath alcohol tests did not indicate any relapse. Another factor contributing to the higher PLMS indices may have been poor compliance regarding magnesium intake. The merely slight increase of serum magnesium levels in this group should, however, be interpreted cautiously, because serum magnesium correlates poorly with tissue magnesium (Elin, 1987), and a possible magnesium loss due to still-impaired renal function (see below) cannot be excluded. Finally, the existence of two subsets of patients cannot be ruled out entirely. The different sleep characteristics of these subgroups may be attributable to some as-yet-undetermined causes on which we can only speculate. The subgroups may simply reflect differences in magnesium metabolism. The high PLMS indices could, however, also hint toward a more substantial disturbance of central neuroadaptation, which may or may not be associated with the magnesium treatment in our study. PLMS are generally regarded as a phenomenon secondary to central nervous dopaminergic dysfunction (Hening et al., 1999; Montplaisir et al., 1991, 2000). PLMS have also been assumed to contribute to sleep disturbances associated with alcohol dependence (Aldrich and Shipley, 1993; Brower and Hall, 2001). In a previous study by our group, a high PLMAI was found to predict 80% of abstainers and 44% of relapsers in a longitudinal study over 6 months (Gann et al., 2002). Because chronic alcohol intake may induce, among other sequelae, a decline of dopaminergic activity (Ollat and Parvez, 1988; Tupala et al., 2001), the persistence of increased PLMS indices might indicate long-lasting or perhaps permanent neurochemical changes. It is also known that PLMS increases with age (Hornyak and Trenkwalder, 2004). The enhancement of PLMS in some primary alcohol-dependent patients would therefore be consistent with the accelerated-aging hypothesis of alcoholism (Gillin et al., 1990b).

A depletion of magnesium in animals was found to lead to an increase of neuronal excitability and to disorganization of sleep—changes similar to those that occur during aging (Depoortere et al., 1993). In humans, an association of severe magnesium deficiency with restless legs syndrome and with parasomnias has been reported (Popoviciu et al., 1991). Conversely, intravenous administration of magnesium before surgery led to a significantly better quality of sleep in a double-blind trial with surgical patients (Tamer et al., 1996). The acute administration of magnesium was found to enhance spindle power in the sleep EEG (Murck and Steiger, 1998). Chronic treatment with a daily dose of 30 mmol of magnesium over 20 days led to a significant increase in slow-wave sleep and delta power in healthy elderly subjects; this suggests a partial reversal of age-related changes in the sleep EEG (Held et al., 2002). Our finding of a significant decrease in sleep onset latency for the entire group and a significant increase of TST and reduction of PLMS during treatment in the PLMS decrease group may also indicate a normalization and stabilization of sleep as a result of the magnesium treatment.

We found only one patient in our study with magnesium deficiency. Five of the 11 patients had increased magnesium excretion even 2 weeks after their last alcoholic drink. Little is known about the time course of recovery of renal dysfunction during abstinence. In the study by De Marchi et al. (1993), renal function improved markedly after 4 weeks of abstinence, but the fractional renal excretion of magnesium decreased more slowly, thus indicating a prolonged renal tubular dysfunction (De Marchi et al., 1993). Therefore, magnesium deficiency could have remained undiscovered in some of the five patients with magnesium loss. Consequently, we cannot draw any conclusion as to whether the magnesium treatment ameliorated a preexisting magnesium deficiency or whether magnesium acted as a pharmacological substance in a yet-unknown fashion. Various pharmacological actions of magnesium have been described. Magnesium has properties of a γ-aminobutyric acid agonist (Schwartz et al., 1994) and is a noncompetitive NMDA antagonist involved in central nervous system excitability (Kuner and Schoepfer, 1996). Furthermore, magnesium seems to play a specific role in higher brain functions, especially those associated with the frontal cortex, which, again, has a significantly higher magnesium content than any other brain structure. Finally, magnesium seems to exert its positive effects primarily under stressful conditions such as sleep deprivation (Chollet et al., 2000; Tanabe et al., 1998). Further research is needed to clarify the relationship between magnesium metabolism and sleep alterations.

In summary, we found a significant decrease of sleep onset latency during magnesium treatment and a significant improvement of subjective sleep quality. TST improved and PLMS indices were reduced in a subgroup of our patients, thus indicating a subset of alcohol-dependent patients who may further profit from magnesium supplementation. Considering the findings of our pilot study, placebo-controlled double-blind trials could be conducted for a better understanding of the pathophysiological changes during the natural course of abstinence and for the recognition of patient groups who could benefit from magnesium treatment.

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