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Movements During Sleep

L-Dopa Therapy of Uremic and Idiopathic Restless Legs Syndrome: A Double-Blind, Crossover Trial

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Summary: We report the effects of a single bedtime dose of L-dopa 100–200 mg on sleep quality, frequency of periodic leg movements (PLM) and daily living in patients with idiopathic and uremic restless legs syndrome (RLS). Seventeen patients with idiopathic and 11 with uremic (on continuous hemodialysis) RLS were evaluated comparatively by polysomnography, actigraphy and subjective ratings in a randomized, controlled and double-blind crossover trial with L-dopa and placebo for 4 weeks each. Neurophysiologic assessments showed significant reduction of the number of periodic leg movements ($p = 0.003$) and the PLM-index ($p = 0.005$) most pronounced during the first 4 hours of bedtime after L-dopa ($p = 0.001$). Subjective evaluation confirmed improvement of sleep quality ($p = 0.002$) and showed significantly higher quality of life during daytime ($p = 0.030$) while the patients received L-dopa therapy. We conclude that L-dopa 100–200 mg proved to be effective in idiopathic RLS and for the first time under controlled conditions in uremic RLS without any severe side effects. **Key Words:** Restless leg syndrome—L-dopa—Therapy—Actigraphy—Polysomnography—Periodic leg movement—PLM-index—Uremia.

Patients with restless legs syndrome (RLS) complain about unpleasant sensory symptoms such as paresthesias, which usually affect the legs, but rarely the arms. The symptoms appear only when the patient is at rest and induce an irresistible urge to move the limbs that results in temporary relief (1,2). Severe sleep disturbances may result because the symptoms occur during the night and cause frequent awakenings (3). As a result, loss of sleep may cause daytime drowsiness, mental exhaustion and reduced quality of daily living (4). An autosomal dominant family history is present in more than one-third of the patients with idiopathic RLS (5–7). Symptomatic RLS can be related to iron deficiency (8), pregnancy (9), treatment with dopamine-receptor blocking agents (2) and, especially, uremia (10). Previous treatment studies in uremic RLS patients have been performed with clonidine (11), clonazepam (12) and in one open trial with L-dopa (13).

In this study, we investigated the beneficial effects of L-dopa on sleep quality and daily living in idiopathic RLS and, especially, in uremic RLS. Above all, we wanted to compare treatment evaluation in RLS patients by neurophysiological methods and subjective ratings and to test the safety of L-dopa, both in idiopathic RLS and patients with uremia.

METHODS

The protocol of this study was reviewed without any objections by the ethical committee of the Medical Department, Klinikum Grosshadern of the Ludwig Maximilian University of Munich.

Design

Following a 2-week baseline period, all patients were treated first with either L-dopa and then placebo or vice versa for 4 weeks in a randomized, controlled,

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double-blind crossover trial. Patients had to stop taking any medication known to have a positive or negative effect on RLS 10 days before baseline. Essential medications (non-psychotropic), especially for uremic patients, were continued. Neurological case history and examination, electrocardiogram (ECG), electromyography (EMG), nerve conduction velocity and polysomnography (PSG) were performed to ensure that the selection criteria were fulfilled. A two-night PSG, including one night for adaptation, was performed to evaluate the diagnosis and inclusion criteria for RLS. At the end of each treatment period, patients were studied again for one night in the sleep laboratory. To evaluate periodic leg movements (PLM) under real-life conditions as well, two additional nights with actigraphical measurements followed each PSG at the patients' homes. Patients subjectively rated their symptoms after each night by filling in a sleep diary, and evaluated their quality of life for the last week of the baseline period and for each treatment period. In addition, patients were monitored by phone calls at least once a week to note any adverse events and to determine whether to increase the dosage of the study drug.

Inclusion criteria

All patients were recruited when they came to the Department of Neurology in the Klinikum Grosshadern because of their restless legs symptoms. The uremic patients were referred either from the dialysis center of the Klinikum Grosshadern or other centers in Munich for differential diagnosis and treatment. In about 70% of the included idiopathic patients and all of the uremic patients, the diagnosis of RLS was made for the first time. About 30% of the idiopathic patients had been under continuous observation at the Department of Neurology. Patients were included if they exhibited RLS symptoms such as 1) paresthesias or other sensory complaints of the lower limbs; 2) an irresistible urge to move the legs; 3) appearance of their symptoms only at rest; 4) increased severity in the evening or at night and 5) stable symptoms during the previous 2 weeks. After rating clinical symptoms at baseline, patients were referred to PSG without any treatment. Patients were included if they had more than five PLM-arousals per hour of sleep, a sleep latency of more than 25 minutes and/or a sleep efficiency index of less than 85%.

Exclusion criteria

Patients with signs of any other sleep disorder on PSG, especially narcolepsy and sleep apnea syndrome, were excluded. Subjects receiving neuroleptic or antidepressant medications or with any severe additional illness or history of drug abuse were also excluded. Pregnant or lactating women and women without safe contraceptive methods were not allowed to participate in this study.

In idiopathic RLS patients, serum chemistry (blood cell count, activated partial thromboplastin time, thrombin time, bilirubin, liver enzymes, calcium, urea, uric acid, creatinine, phosphate, lactate dehydrogenase, vitamin B12, folic acid, iron, thyroid stimulating hormone, T3/T4, glucose, transferrin, ferritin) had to be in the normal range and no further neurological disorder present. An EMG and nerve conduction studies were performed to exclude peripheral neuropathy or radiculopathy. In uremic patients, moderate peripheral neuropathy with slow nerve conduction velocity and a deviation from standard laboratory parameters were tolerated. Uremic patients who received maintenance dialysis in three courses per week were given regular iron, erythropoietin and folate supplements.

Dosing

Each study capsule contained either L-dopa 100 mg plus benserazide 25 mg (Madopar® Standard, Hoffman-La Roche AG, Grenzach, Germany) or placebo. Medication was taken 1 hour before bedtime. Initial therapy consisted of one capsule. Patients could increase the dose by another capsule if they considered that their sleep had not improved sufficiently in the first 2 weeks of treatment. This increased dose then remained unchanged for the rest of that treatment period; in the second crossover period therapy again started with one capsule. Subjects were instructed to avoid the simultaneous intake of protein or medication, which is known to inhibit the absorption of L-dopa.

Polysomnographic studies

At baseline and at the end of both treatment periods, PSG recordings of each patient were made for one night (11 p.m.–7 a.m.). Studies included monitoring of electroencephalogram (EEG) (C3–A2, C4–A1), electrooculogram [according to Rechtschaffen and Kales (14)], chin EMG, EMG of both anterior tibialis muscles, and electrocardiogram (ECG). [For details of PSG methods, see Pollmächer and Schulz (15).] At baseline, respiration, oronasal airflow, respiration effort and oxygen saturation were monitored by standard methods. Sleep scoring was also done by standard methods (14). PLM were scored only if they were part of a series of at least four consecutive movements lasting 0.5–5 seconds, with an intervene interval of 4–90 seconds (16).

We have demonstrated that the interrater reliability of PLM is high (15), and the same methods have been applied for this investigation. We evaluated the total number of PLM and computed the PLM index (number of PLM per hour of sleep) separately for the first (hours 1–4) and second (hours 4–6) halves of the night in the treatment and placebo periods. In addition we calculated the PLM arousal index [number of PLM associated with arousals per hour of sleep; for further definition see Pollmächer and Schulz (15)].

Actigraphy

In parallel to the PSG and for two additional nights, PLM were recorded by an actigraph during each period. A newly developed actigraph (Movoport, Rimkus, Munich) was adjusted to the requirements necessary to record and measure PLM (Kazenwadel et al., unpublished). The patients started recording only when they went to bed, and the periods of walking around during the nocturnal recording were excluded from the evaluation. Scoring of PLM was performed automatically using a digital threshold, and then reviewed by a trained investigator. The frequency of PLM was calculated using the same criteria as defined for EMG scoring of PLM. Additionally, total time in bed was calculated to compute the PLM-index from actigraphical data.

Subjective ratings

At baseline and at the end of each treatment period, patients rated their quality of life, concerning well-being and complaints during the previous week, using modified 50-mm Hamburger Visual Analogue Scales (17). After each night of recording, patients also filled in a sleep diary rating the following symptoms: global assessment of sleep (from very bad to very good night), sleep latency, frequency of awakenings and urge to move the legs at the time of falling asleep, during the night and during the following day (scale: 0 = not present to 10 = very strong).

Physician's ratings of RLS

The physician in charge had to rate the severity, the change of the disease severity, the therapeutic effects and the tolerability of treatment by use of the Clinical Global Impressions (CGI) (18) at the end of each crossover period.

Safety evaluation

Safety of L-dopa therapy was assessed according to the frequency and type of adverse events, clinically relevant changes in laboratory data and premature discontinuation of study participation. Adverse event recording was based on spontaneous reporting and made use of clear-cut definitions of the adverse events' classification (serious versus nonserious), intensity, relationship to drug treatment, frequency, course and therapeutic intervention.

Statistical analysis

Statistical evaluation was performed as a standard crossover analysis (19), in which the effects of treatment, carryover and period effects were estimated. The number of PSG measured PLM related to total time in bed (PLM-index, hourly basis), duration of sleep and subjective rating of sleep quality were tested by Student's t test or Wilcoxon U test in a hierarchical procedure. This approach enabled the total probability of type I error of alpha = 5%. All further endpoints were analyzed by t test or Wilcoxon U test and interpreted (reporting p values). Likewise, the results of idiopathic and uremic patients were compared by multiple t tests. In the Results section of this paper, descriptive statistics were pooled across medications of both crossover sequences, whereas p values refer to the results of the genuine crossover analysis (treatment effect). In addition, PLM index was calculated separately for 1-hour periods of the night and compared by t tests in the crossover analysis.

RESULTS

Subjects

Out of the initial 32 white patients, 28 (18 men, 10 women; mean age 52 ± 10 years, range 29–73 years) finished the study according to the protocol. Of these 28 patients, 17 had idiopathic RLS and 11 had uremic RLS and were receiving maintenance hemodialysis (Table 1). Two other patients, both with uremia, discontinued prematurely due to intermittent diseases (Wegener's granulomatosis, deterioration of general condition), which were considered not to be related to the study drug. Finally, two additional subjects were not included in the analysis, as the PSG inclusion criteria were not met. The characteristics of the 28 valid patients are reported in Table 1.

Dosage

Fifteen patients receiving L-dopa and five patients receiving placebo took only one capsule of the study drug during the respective crossover period. In 13 patients on L-dopa and 23 on placebo, the dosage was increased to two capsules (L-dopa 200 mg plus ben-

TABLE 1. *Clinical characteristics of patients with idopathic and symptomatic (uremic) RLS*

Characteristics	Idiopathic RLS	Uremic RLS	All patients
Number	17 (61%)	11 (39%)	28 (100%)
Age (mean)	53 ± 9 years	49 ± 11 years	52 ± 10 years
Age (range)	37–73 years	29–66 years	29–73 years
Sex (males)	12 (71%)	6 (54%)	18 (64%)
Duration of RLS (mean)	14 ± 12 years	3 ± 3 years	10 ± 10 years
Duration of hemodialysis (mean)	—	3 ± 2 years	—
Sensory symptoms of legs (n)	17 (100%)	11 (100%)	28 (100%)
Sensory symptoms of arms (n)	8 (47%)	7 (64%)	15 (54%)
Motoric symptoms: cramps (n)	9 (53%)	3 (27%)	12 (43%)
Motoric symptoms: jerks (n)	6 (35%)	6 (54%)	12 (43%)
Patients' ratings			
Severity of RLS (scale 0–10 = severe)	8.2 ± 1.2	7.3 ± 1.9	7.9 ± 1.9
Sleep latency (mean)	69 ± 77 min	97 ± 92 min	80 ± 83 min
Frequency of awakenings (mean)	4.1 ± 3.7	3.2 ± 2.6	3.7 ± 3.3
Daytime drowsiness present (n)	10 (59%)	8 (72%)	18 (64%)
Positive family history (n)	9 (53%)	1 (9%)	10 (36%)
Treatment within last year			
None (n)	4 (24%)	1 (9%)	5 (18%)
L-dopa (n)	6 (35%)	6 (54%)	12 (43%)
Benzodiazepines (n)	2 (12%)	4 (36%)	6 (21%)
Opioids (n)	1 (6%)	0	1 (4%)
Other (n)	9 (53%)	2 (18%)	11 (39%)

RLS = restless legs syndrome.

serazide 50 mg or placebo). Eleven patients received two capsules of placebo while their L-dopa dosage of one capsule was not increased; in only one patient, one capsule of placebo, but two capsules of L-dopa were required ($p = 0.004$ for dose adjustments, McNemar test). The mean L-dopa dosage at the end of each crossover period was 146 ± 50 mg, or 1.46 ± 0.5 capsules. During placebo treatment, the mean number of capsules was 1.82 ± 0.39 ($p = 0.005$).

Efficacy

Crossover analysis of the three primary endpoints showed superior efficacy of L-dopa compared with placebo for the following parameters: 1) number of PLM during time in bed (PLM index) was reduced (L-dopa 45.3 ± 45.9 versus placebo 63.0 ± 47.8; $p = 0.005$); 2) sleep time was prolonged by more than half an hour (316 ± 94 minutes versus 281 ± 128 minutes, respectively; $p = 0.045$, Wilcoxon test) and 3) subjective quality of sleep during the last week was estimated to be better with L-dopa (4.9 ± 1.8) compared with placebo (3.0 ± 2.3, $p = 0.002$; Table 2).

Polysomnography. The absolute number of PLM during time in bed was smaller during L-dopa treatment than placebo (327 ± 347 versus 459 ± 351, respectively; $p = 0.003$). As shown in Fig. 1a, the superior efficacy of L-dopa lasted only for the first 4 hours after the drug was taken and disappeared later in the night; in the statistical analysis (Table 2), the PLM index was reduced in the treatment period in hours 1–4 ($p = 0.001$) and was not different from placebo in hours 5–6 ($p = 0.232$). In parallel, the PLM index of the total night (see Methods) was decreased by L-dopa (45 ± 46 versus 63 ± 48, respectively; $p = 0.005$) as well as the PLM arousal index (41.8 ± 42 versus 55.9 ± 40.7; $p = 0.020$). The sleep efficiency index ($p = 0.300$) and frequency of nocturnal awakenings were similar in both treatments ($p = 0.231$). The percentage of sleep stages 3 and 4 together was 10% of the entire sleep stages in the baseline and placebo periods and was not significantly different from the L-dopa period ($p = 0.627$). Sleep latency was only slightly improved by L-dopa (43 ± 34 minutes versus 70 ± 90 minutes; $p = 0.118$).

Actigraphy. The evaluation of PLM and sleep by actigraphy during the nights in the sleep laboratory yielded results similar to those obtained by PSG concerning the decrease of the number of PLM ($p = 0.094$) and the PLM index ($p = 0.077$) in the treatment period compared with the placebo period. As demonstrated in Fig. 1b, the actigraphic timecourse of PLM per hour matches the PSG data in both treatment groups and further confirms the 4-hour-efficacy of L-dopa treatment. Using the special advantage of actigraphy to measure leg movements at the patients' homes, the stable reduction of PLM was obvious (number: 230 ± 256 versus 324 ± 262, $p = 0.003$; PLM index: 30.3 ± 33.1 versus 42.1 ± 33.4, $p = 0.005$) in the combined data from three consecutive nights (one night in the sleep laboratory, two nights at home).

Subjective ratings of sleep and RLS. Regarding sleep features, patients reported fewer nocturnal awakenings while receiving L-dopa than placebo in their sleep di-

TABLE 2. *Treatment effects in 28 RLS patients receiving L-dopa (mean dosage 146 ± 50 mg) and placebo. In interpreting the effects in the subgroups of idiopathic and sympomatic RLS patients, the small number of sample sizes (17/11) must be taken into account.*

Efficacy criteria	Idiopathic RLS		Uremic RLS		All RLS patients		p
	L-dopa	Placebo	L-dopa	Placebo	L-dopa	Placebo	
Objective methods							
Frequency of PLM (polysomnography, total night)	244 ± 244	309 ± 217	477 ± 458	727 ± 394	327 ± 347	459 ± 351	0.003
PLM index (polysomnography, total night)	32 ± 31	44 ± 33	69 ± 59	97 ± 53	45 ± 46	63 ± 48	0.005
PLM index (mean, hours 1–4)	31 ± 32	48 ± 43	69 ± 61	119 ± 56	44 ± 46	72 ± 57	0.001
PLM index (mean, hours 5–6)	31 ± 48	34 ± 32	63 ± 71	91 ± 71	42 ± 57	54 ± 55	0.232
PLM arousal index (polysomnography)	29 ± 28	40 ± 30	64 ± 54	84 ± 42	42 ± 42	56 ± 41	0.020
Frequency of PLM (actigraphy, 3 nights, total night)	119 ± 175	208 ± 183	362 ± 283	464 ± 282	230 ± 256	324 ± 262	0.003
PLM index (actigraphy, mean of 3 nights, total night)	15 ± 22	28 ± 23	49 ± 36	60 ± 36	30 ± 33	42 ± 33	0.005
PLM index (mean, hours 1–4)	13 ± 17	32 ± 23	49 ± 39	77 ± 47	30 ± 34	52 ± 42	0.001
PLM index (mean, hours 5–6)	18 ± 29	16 ± 27	42 ± 43	52 ± 40	29 ± 38	33 ± 38	0.319
Patient's sleep diary							
Frequency of awakenings per night	1.8 ± 0.8	2.3 ± 1.3	2.0 ± 0.7	2.4 ± 0.6	1.8 ± 0.8	2.4 ± 1.1	0.043
Quality of sleep (scale: 0–10 = good)	4.8 ± 1.9	3.1 ± 2.4	5.0 ± 1.8	2.9 ± 2.3	4.9 ± 1.8	3.0 ± 2.3	0.002
Severity of RLS during night (scale: 0–10 = bad)	3.6 ± 2.5	5.5 ± 3.1	3.7 ± 3.4	4.6 ± 4.3	3.7 ± 2.8	5.2 ± 3.6	0.018
General condition (scale: 0–10 = good)	4.8 ± 2.0	3.7 ± 2.0	5.1 ± 1.5	4.2 ± 1.7	4.9 ± 1.8	3.9 ± 1.9	0.049
Physician's CGI rating							
Severity (8 = severe)	6.2 ± 1.0	6.4 ± 0.9	6.3 ± 1.1	6.5 ± 1.1	6.2 ± 1.0	6.5 ± 1.0	0.045
Global assessment of change (8 = worse)	3.7 ± 1.6	4.9 ± 1.7	3.7 ± 1.3	4.6 ± 2.1	3.7 ± 1.5	4.8 ± 1.8	0.025
Subjective quality of life							
Life satisfaction (50 = high)	27.5 ± 6.7	24.1 ± 4.4	24.2 ± 10.1	17.4 ± 9.3	26.2 ± 8.1	21.6 ± 7.3	0.016
Negative feelings and complaints (50 = high)	17.8 ± 6.9	22.3 ± 8.7	21.6 ± 9.6	24.3 ± 10.4	19.2 ± 8.1	23.0 ± 9.2	0.024

CGI = Clinical Global Impressions; PLM = periodic leg movements.

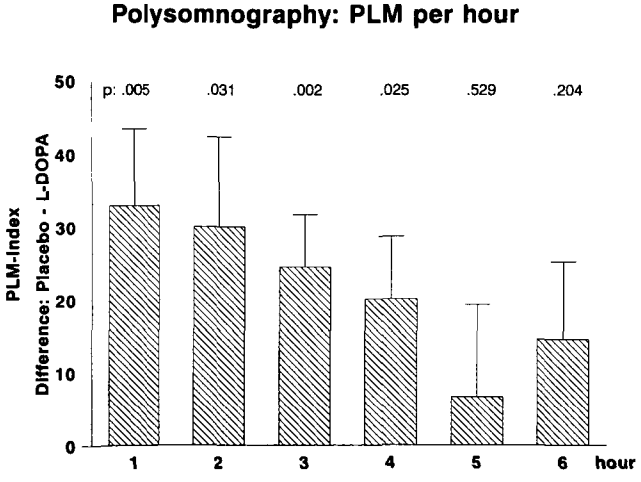

FIG. 1a. Polysomnographically measured difference of the PLM-index (periodic leg movements per hour) during L-dopa and placebo treatments during one night in the sleep laboratory. There is a remarkable superior efficacy of L-dopa during the first 4 hours of the night.

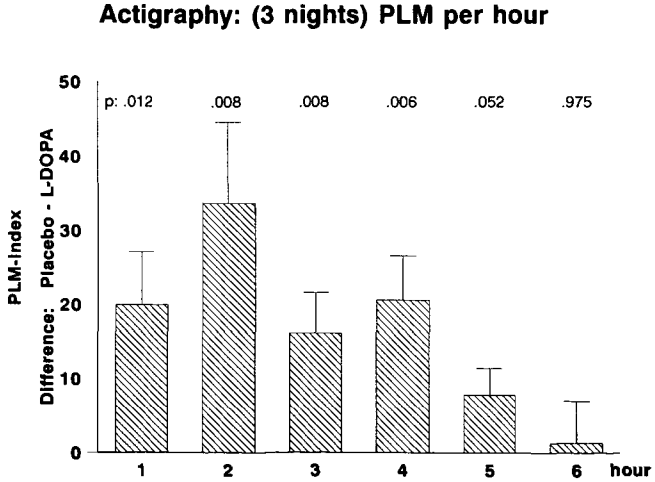

FIG. 1b. Actigraphically measured difference of the PLM-index (periodic leg movements per hour) during one night in the sleep laboratory and two consecutive nights at home during L-dopa and placebo treatments. Note the similar results to polysomnography, confirming the 4-hour-efficacy of L-dopa.

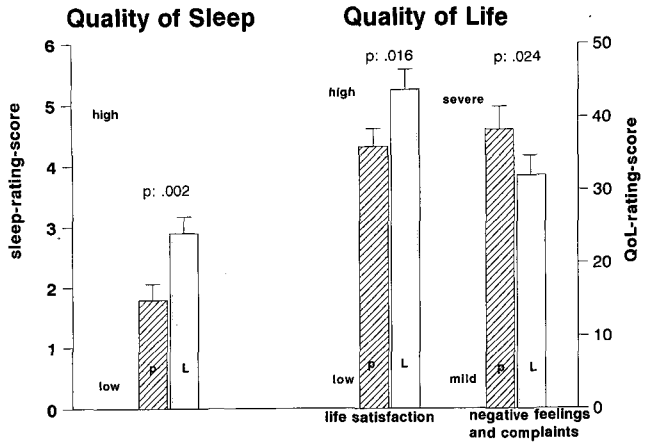

FIG. 2. Patients' ratings of quality of sleep and quality of life in questionnaires answered during L-dopa and placebo treatments.

aries (p = 0.043) and awoke less often with symptoms of restless legs, such as an urge to move or sensory symptoms (p = 0.086). There were no marked differences in sleep latency (p = 0.112) and in sleep time until the first awakening (p = 0.203). Global ratings of RLS for the last week of each crossover period were only slightly improved by L-dopa during the time of falling asleep (p = 0.158), but markedly improved during the night (p = 0.018). The patients' general subjective conditions during the total crossover period were better with L-dopa than with placebo (p = 0.049).

Subjective ratings of quality of life. Using 13 visual analogue scales, which can be subdivided into scales measuring life satisfaction, and negative emotional states and complaints, patients estimated their quality of life during the last week of a 4-week-treatment period. L-dopa improved their general well-being (p = 0.023), satisfaction with their efficiency at work (p = 0.019) or during leisure time (p = 0.017). Mood (p = 0.003) was also improved by the active drug and tiredness was less pronounced (p = 0.041). Combining these scales into two categories, L-dopa showed better results in both categories, "life satisfaction" (p = 0.010), and "negative feelings and complaints" (p = 0.024, Fig. 2).

Physician's ratings of severity of RLS. In two of the three efficacy-related scales of the CGI, severity (p = 0.045) and changes in disease severity (p = 0.025), L-dopa was estimated to have better effects than placebo. Regarding the specific therapeutic effect of both study drugs (item 3), there was only a slightly better nonsignificant efficacy of L-dopa compared with placebo (p = 0.120).

Comparison of idiopathic and uremic patients. In Table 2, the results of the statistical analysis of the most important efficacy indicators for idiopathic and uremic patients are compared. In interpreting this table, the decreased power of these analyses due to small sample sizes must be taken into account. Statistical comparisons between the groups were performed by analyzing differences between L-dopa and placebo, using the pooled data. The objective measures of sleep and RLS, the quality of life assessment and the physicians' evaluations are comparable for both groups. They hint at a superior efficacy of L-dopa compared with placebo in both diagnostic groups.

Safety

Adverse events. A total of 33 adverse events were reported in 15 patients, 20 (12 patients) receiving L-dopa and 13 (8 patients) during placebo administration. Nine adverse events with L-dopa therapy and six events with placebo treatment were seen as at least "possibly" related to therapy. Only one of these events, agitation after caffeine intake that appeared during L-dopa therapy, was estimated as "severe". The most frequent adverse events reported with L-dopa therapy were headaches (four events; placebo, none), dry mouth (three events; placebo, one) and gastrointestinal symptoms (three events; placebo, two). In one uremic patient, Wegener's granulomatosis was diagnosed, requiring hospitalization and premature discontinuation of the study. One other uremic patient left the study because of increased generalized weakness.

Changes in laboratory data. In intragroup analysis (sign test), no systematic changes in laboratory data could be detected while the patients received L-dopa.

Physicians' global assessment of tolerability. In the CGI, tolerability was estimated as slightly worse for patients receiving L-dopa than for those receiving placebo (p = 0.066), reflected in the higher frequency of adverse events with L-dopa therapy.

DISCUSSION

Efficacy of L-dopa

L-dopa has been established as a standard treatment regimen for RLS (20–24). Besides L-dopa, dopamine agonists (25), benzodiazepines (26,27), opioids (28,29), carbamazepine (30,31) and clonidine (32) are proposed to be efficacious in the treatment of idiopathic RLS. This randomized, placebo-controlled crossover trial with a substantial sample size of both idiopathic and uremic RLS patients confirmed the efficacy of L-dopa in RLS-related sleep disturbances and found this to apply to uremic RLS patients as well. A 4-week treatment with one dose per night of L-dopa 100–200 mg plus benserazide 25–50 mg improved the total number of PLM as well as the PLM index and PLM arousal index. There was no rebound effect in the second half of the night, indicated by the stable number of PLM at the end of the nights in the treatment and placebo

periods (Fig. 1a). The same result was replicated during the following two nights at home by a newly developed actigraph that allows the reliable registration of PLM.

Although sleep laboratory studies could not objectively measure the beneficial effect of L-dopa on "sleep efficiency", the patients reported this effect quite reliably in their diaries. These findings are consistent with the two controlled studies of L-dopa that revealed a significant reduction of PLM and a subjective improvement of sleep, but no improvement in sleep efficiency (20,33). Using a rather strict dosing regimen without a second dose per night, we wanted to detect the minimal effective dosage of L-dopa and to characterize the efficacy profile of standard L-dopa treatment in idiopathic RLS and especially in uremic RLS patients. In previous studies (22,23,33,34), patients received a single dose of L-dopa, whereas in the first controlled study with six patients a second dose of L-dopa after 4 hours of sleep was applied to avoid "rebound effects" (20,35). This rebound effect has been observed in previous studies (20,35) and has been described as morning leg restlessness after long-term L-dopa treatment in some patients (36). In our study, the PLM index for the second half of the night did not indicate any rebound effect; that means an increase of PLM after the first half of the night in the L-dopa period compared to the placebo period.

The efficacy of L-dopa in the first 4–5 hours of sleep probably reflects the dopamine plasma concentration after treatment with a single dose of L-dopa plus benserazide (37). In our study, a variable dose of L-dopa (100–200 mg) achieved a significant reduction of PLM in the first 4–5 hours of sleep. This result has been confirmed by Kaplan et al. (33), who compared carbidopa/levodopa with propoxyphene in a controlled trial of six patients with idiopathic RLS. The effects of PLM reduction and improved sleep were particularly pronounced in the first 3 hours of sleep and superior to the propoxyphene treatment. Although the patients reported an improvement of their sleep in general during the L-dopa period, some patients needed a second dose or a sustained-release preparation of L-dopa to achieve prolonged sleep without awakenings. Preliminary data from an open study showed a reduction of self-rated nocturnal awakenings during combination therapy with L-dopa standard and the sustained-release preparation of L-dopa plus benserazide (Madopar HBS®) (38). We are currently investigating the benefits of this combination therapy in a controlled study.

Stability of L-dopa treatment

Actigraphic measurements confirmed the stable effect of the evening dose of L-dopa during the following nights at home (Fig. 1b) (Kazenwadel et al., unpublished). The reliability of actigraphic recordings of PLM was almost as high as that of polysomnographically computed PLM and also reflected the treatment effect of L-dopa when the patients slept at home. With this newly developed method, treatment effects—at least in RLS or PLM patients—can now be monitored by the patient at home, and reliably reflect the patient's individual sleep habits and monitor long-term drug effects. Long-term L-dopa studies showed a 2-year stability of the dosage regimen (24) and a more than 70% long-term response with dopaminergic treatment in 1 year (38).

Uremic RLS patients and quality of life

Dialysis patients suffer from a markedly reduced quality of life because of their treatment efforts, concomitant diseases and other problems such as pruritus or diet. An additional, often severe RLS further limits the patients' well-being. Clinical characteristics indicate even more severe symptoms for uremic patients, and involuntary motor symptoms during the daytime, especially during the hemodialysis, are present in uremic patients as well (39). The increased quality of daily living with L-dopa treatment is of major interest in chronic uremic patients. We found a marked improvement in the quality of daily living during the L-dopa treatment period. This concerned the patients' general well-being as well as specific items during leisure time and at work (Fig. 2). Interestingly, the patients felt their mood to have improved as well (Fig. 2). One open study showed a beneficial effect of L-dopa treatment in uremic patients (13). Patients noticed subjective relief from sensory symptoms when treated with L-dopa 100–200 mg plus carbidopa up to three times daily. At the moment these improvements are validated only for the short-term treatment with L-dopa and have to be proven in long-term therapy.

No severe side effects were noticed in uremic patients. A recent study monitored the application of L-dopa 100 mg and benserazide 25 mg in dialysis patients without RLS, for safety reasons. The authors found an increase of dopamine and 3-*O*-methyldopa in uremic patients compared with controls, but no clinical, acute or prolonged side effects of L-dopa (Ch. Crevoisier, Hoffmann La Roche, personal communication).

CONCLUSIONS

We suppose that L-dopa itself improves the motor and sensory symptoms of RLS, and the duration of its efficacy matches the pharmacokinetic profile of L-dopa plus benserazide. These observations proved to be right in both idiopathic and uremic RLS patients and dem-

onstrate the efficacy during a short-term treatment period, as done in most controlled studies (20,25,29,33). Benefits for long-term treatment with L-dopa can be assumed from previous open studies (24,36). A single dose of L-dopa plus benserazide is therefore useful in treating sleep disturbances during the first half of the night and in mild RLS symptoms. Otherwise, combination therapy with a standard and sustained-release preparation of L-dopa will probably further improve sleep quality in RLS patients.

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