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ORIGINAL COMMUNICATION

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Treatment of idiopathic restless legs syndrome (RLS) with slow-release valproic acid compared with slow-release levodopa/benserazid

A randomized, placebo-controlled, double-blind, cross-over study

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Abstract We aimed to compare the efficacy of valproic acid (VPA) on paresthesias and sleep in RLS to that of levodopa (LD). Twenty patients with idiopathic restless legs syndrome (RLS) were treated with 600 mg slow-release VPA and 200 mg slow-release LD + 50 mg benserazid in a randomized, placebo-controlled, cross-over, double-blind setting with polysomography (PSG) at the end of each 3-week treatment periods. There was no major difference between the efficacy of valproic acid or LD. Periodic leg movements in sleep (PLMS) and PLM arousal index (PLMAI) significantly decreased with LD ($p \leq 0.005$). However, LD, but not VPA, significantly increased arousals not associated with PLMS ($p = 0.002$). Decrease of intensity and duration of RLS symptoms were more pronounced with VPA ($p \leq 0.022$) than with LD (NS). We conclude that slow-release VPA provides a treatment alternative for RLS.

Key words restless legs syndrome · valproic acid · polysomnography

Introduction

Restless legs syndrome (RLS) causes at rest leg paresthesias accompanied by an urge to move the legs [2] especially in the evening and night. RLS is often associated with periodic limb movements in sleep (PLMS) [2]. Drugs of first choice in RLS are dopaminergics [7]. Recently, valproic acid (VPA) has been shown to consolidate sleep in patients with PLMS but without RLS [5]. We hypothesized that VPA is as effective as levodopa (LD) on paresthesias and sleep in idiopathic RLS when compared with placebo.

Methods

The study protocol was approved by the ethics committee of the University of Munich, Germany and supported by Sanofi pharmaceutical industry. All patients gave their written informed consent before the study inclusion.

Protocol

Inclusion and exclusion criteria

The International Restless Legs Study Group (IRLSSG) minimal diagnostic criteria had to be fulfilled [10]. Patients were included if they had a PLMS index (PLMI) of > 10/h of total sleep time (TST) and had suffered from RLS daily for at least six months prior to the study. Patients with signs of any other sleep disorder or severe additional disease and polyneuropathy, pregnant or lactating women and women without safe contraception were excluded. Patients taking any medication suggested as treatment for RLS had to stop this medication five days prior to study entry. Any other medication had to be stable throughout the study.

Patients

Twenty patients with idiopathic RLS were included in the study (12 women, 8 men, age: 58.9 ± 6.9 years (range: 41–74). Two patients had been taking doxepine (50 mg per day), which remained stable throughout the study; none of the other patients took any psychoactive drug. Mean disease duration was 17.2 ± 15.5 years (range: 4–54). Twelve patients (60 %) reported a history for RLS in their first degree relatives. The baseline polysomnography (PSG) revealed the following: TST: 341.3 ± 66.5 min., wake after sleep onset (WASO): 91.3 ± 52.7 min., sleep efficiency (SE): 79 ± 11.3 %, PLMI: 42.3 ± 40.7/h, total

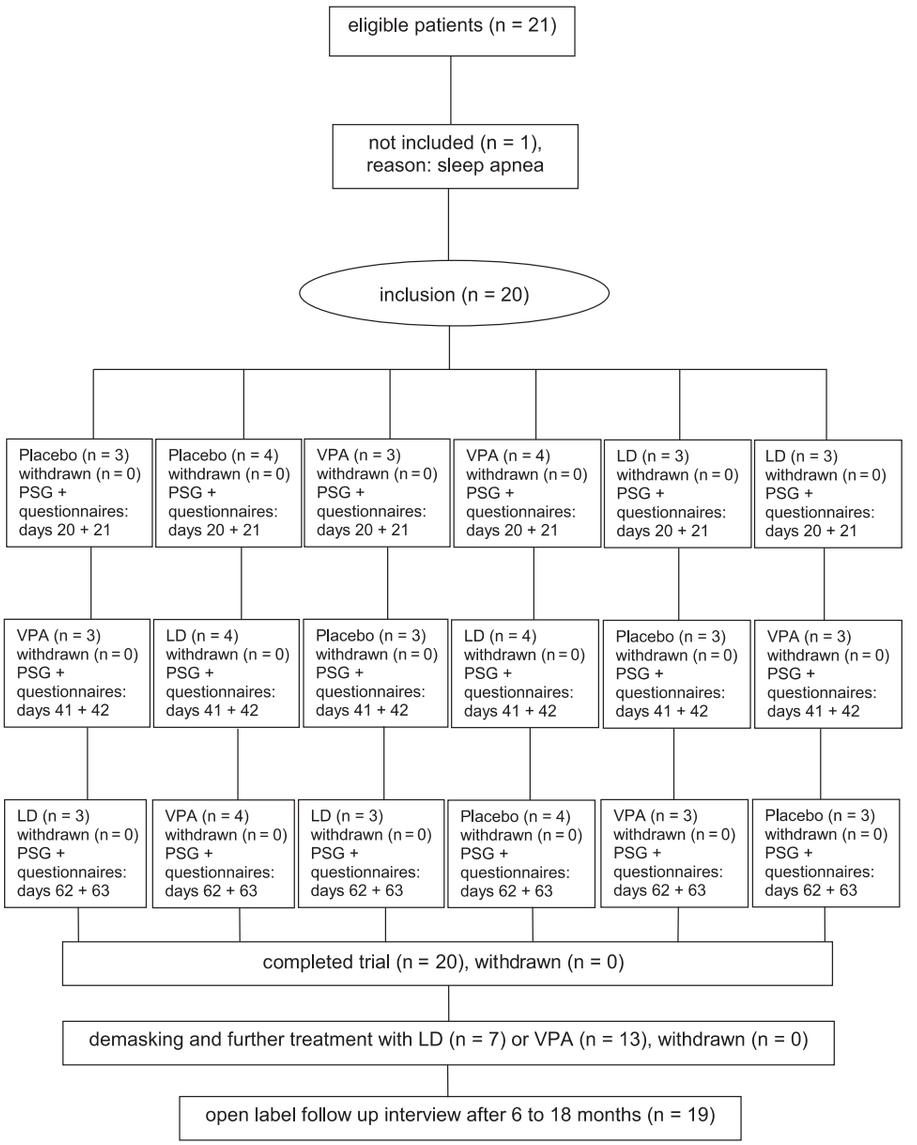

Fig. 1 Figure 1 shows the flow diagram of the study design (*VPA* valproic acid; *LD* levo-dopa; *n* number of patients)

arousal index (TAI): 30.6 ± 15.3/h, PLM arousal index (PLMAI): 11 ± 11.8/h.

Design (Fig. 1)

Before study entry, all patients underwent a two-night standard PSG. PSGs were scored visually according to a method described previously [6]. After study entry, all patients received placebo, 600 mg slow-release VPA and 200 mg slow-release LD (+ 50 mg benserazid), each for three weeks. Doses of VPA/LD were started with 300/100 mg and increased to 600/200 mg after two days. Patients were instructed to take their medication 90 minutes before bedtime. At the end of each 3-week treatment period, patients underwent a two-night PSG, reported any side effects, and filled out a 24-hour RLS rating scale. This scale documented the duration of their RLS symptoms (paresthesias and/or urge to move) in minutes per hour (filled out for each hour of the 24-hour time period), and the overall intensity of the symptoms during the 24 hours using a 0–10 visual analogue scale, 10 being the most severe. All patients underwent complete physical examination at baseline and the study end. After the study, each patient could continue on treatment with the study medication that was determined by both subject and investigator, according to best reduction in RLS symptoms and least side effects. An open label follow up, where patients were asked about their satisfaction with their current RLS therapy was performed 6 to 18 months after the study end over a time period of 12 months. Blood chemistry and nerve conduction measures were analysed to exclude symptomatic forms of RLS. Blood levels of VPA and liver enzymes were determined at each study visit. Primary outcome measures were intensity and duration of RLS symptoms as given in the questionnaires, and sleep efficiency and PLMS as measured in the PSG. Assuming an increase of 10 % in sleep efficiency and a reduction of 30 % of the other primary outcome variables with LD or VPA, a sample size of 20 patients was estimated to be sufficient to find significant differences with a power of at least 0.8 at a signifi-

cance level of at least 0.05. Secondary outcome variables were number of side effects, percentages of sleep stages, arousal indices, sleep latency and long-term efficacy. Patients had to stop the study if serious side effects were present.

Assignment

The treatment sequence was defined for each patient by the department of pharmacy secretly. Six different treatment sequences were individually randomized to the 20 patients.

Masking

Forty two similar looking and similar tasting capsules (100 mg LD/25 mg benserazid, 300 mg VPA or 200 mg placebo) were distributed by the department of pharmacy at the beginning of each three week treatment period, when requested by the blinded executor mentioning patient number and treatment session. When a patient had completed the study, the code of this patient was broken by the department of pharmacy and told to the physician who further treated the patient. Another physician who distributed the drugs, attended the PSGs, took blood samples, asked side effects, collected questionnaires and did the statistical analyses did not know about the treatment sequences until the end of the study, when statistical analyses were completed.

Statistical analysis

Data were tested for normal distribution with the Kolmogorow-Smirnov test. Because most of the data were not normally distributed, the Friedman and Wilcoxon test for paired differences was applied to test differences between subjective ratings and PSG data with different drug conditions. The chi-square test was used to test differences between dichotomous variables (number of side effects, long term efficacy). A p value of < 0.05 was considered significant. Values are given as mean ± standard deviation, if not stated otherwise.

Results

The statistical tests performed were exploratory and not corrected for multiple testing. No sequence effect of the different treatment sequences was observed.

Side effects

There were similar side effects between the three groups and nine patients reported side effects with placebo therapy. That indicates successful blinding at least partially. Nine of the 20 patients suffered from side effects with VPA, 9 with placebo and 13 with LD therapy (NS). Side effects are summarized in Table 1.

Laboratory tests

VPA was undetectable in the serum with LD or placebo treatment. With VPA treatment VPA blood levels taken at seven am before breakfast were 40 ± 13.3 µg/ml (range: 17.6–75.4). All patients had normal γ-GT (with VPA: 12.1 ± 6 U/l, range: 4–30 U/l). At baseline, ferritin (150.2 ± 113.3 ng/ml (range: 36–480), Vitamin B12, creatinine, folate, hematological and thyroid hormone levels were normal.

PSG data

TST, WASO and PLMAI revealed significantly better values in the placebo than on the baseline night ($p \leq 0.025$). Table 2 shows PSG results.

Subjective rating of RLS symptoms (Table 2)

In contrast to LD, VPA significantly decreased the subjectively rated intensity of RLS complaints and duration of RLS symptoms during a 24-h time period. This decrease in RLS symptoms was based mainly on a decrease between 0:00 and 8:00 h (0:00–4:00: $p = 0.016$; 4:00–8:00: $p = 0.046$). LD significantly decreased RLS symptoms between 0:00 and 4:00 h, but did not significantly decrease RLS symptoms over the 24-h time period. In fact,

Table 1 Side effects

placebo	slow-release valproate 600 mg	slow-release levo-dopa 200 mg
dizziness (n = 2), drowsiness (n = 3), headache (n = 6), nausea (n = 1), lower back pain (n = 1), air in the stomach (n = 1), none (n = 11)	feeling of pressure in the chest (n = 1), flatulence (n = 1), difficulties falling asleep (n = 2), drowsiness (n = 3), edema (n = 1), finger pain (n = 1), headache (n = 2), blurred vision (n = 1), hand tremor (n = 1), hair loss (n = 1) none (n = 11)	nausea (n = 2), augmentation (n = 4), drowsiness (n = 4), dizziness (n = 1); flatulence (n = 1), hard stool (n = 1), belly ache (n = 1), diarrhea (n = 1), hair loss (n = 1), weight gain (n = 1), headache (n = 3), cold hands (n = 1), apathy (n = 2), none (n = 7)

n number of subjects

Table 2 PSG parameters and RLS subjective rating. Comparison to placebo

	slow-release valproate 600 mg	slow-release levo-dopa 200 mg	placebo
Total sleep time (min.)	378.8±55.1 NS	367.3±77.5 NS	381.9±51.5
Sleep efficiency (%)	78.5±9.3 NS	81.7±7.5 NS	78.5±10.2
Latency to stage 2 (min.)	40.6±28.8 p = 0.044	25.0±16.9 NS	29.7±26.8
REM latency (min.)	98.9±56.2 NS	119.7±56.3 NS	96.5±66.2
Wake after sleep onset (min.)	18.5±15.4 NS	17.5±10.7 NS	21.8±20.6
Stage 1 (min.)	32.5±15.0 NS	34.1±19.8 NS	31.4±9.8
Stage 2 (min.)	205.2±44.3 NS	187.6±48.4 NS	209.9±51.8
Stage 3 + 4 (min.)	62.3±38.7 NS	70.6±42.7 NS	64.4±45.9
Stage REM (min.)	78.3±23.9 NS	74.8±22.1 NS	76.0±25.4
PLMI (n/hr TST)	38.0±32.3 NS	19.9±23.2 p = 0.005	43.2±36.9
PLMAI (n/hr TST)	15.3±12.9 NS	9.6±13.5 p = 0.002	21.3±16.1
TAI (n/hr TST)	24.7±10.4 NS	24.7±12.0 p = 0.040	30.8±14.2
AI (n/hr TST)	9.5±5.9 NS	15.1±5.7 p = 0.002	9.4±4.0
RLS intensity score	3.8±2.5 p = 0.022	4.4±2.5 NS	5.5±1.7
RLS duration (min. during 24 hours)	103.5±225.5 p = 0.007	155.0±235.1 NS	195.8±224.2

n number; *h* hour; *PLMI* periodic limb movement index; *PLMAI* PLM arousal index; *TAI* total arousal index; *AI* arousal index without PLMAI; *RLS* restless legs syndrome; *REM* rapid eye movement sleep

with LD therapy there was a statistically non-significant trend of increased RLS symptoms between 12:00 and 24:00 hrs (Fig. 2).

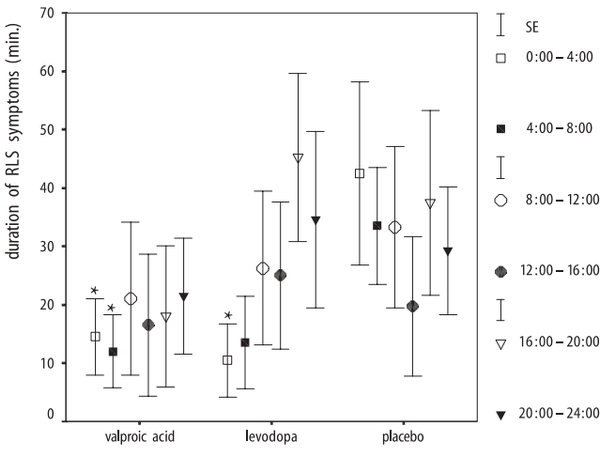

Fig. 2 Figure 2 shows the time course of RLS symptoms during the day and night period with different treatment conditions (*SE* standard error of the mean)
* statistically significant ($p < 0.05$), when compared to placebo

Follow up

After completion of the study, when the double-blind code was broken, 7 patients were recommended for further treatment with LD and 13 with VPA. Although LD reduced RLS symptoms more than VPA, one patient was selected to receive VPA because of increased daytime sleepiness from LD therapy. Follow up 6 to 18 months after the study end was achieved in 19 patients and revealed that VPA was still effective in 75 % (9 out of 12 patients) whereas only 29 % (2 out of 7 patients) were still satisfied with LD ($p = 0.048$).

Discussion

VPA accumulates gamma-amino-butyric acid (GABA) in different brain regions and inhibits sodium and calcium streams at nerve cell binding sites [3]. Slow-release VPA reaches peak levels in the serum 90 to 120 minutes after oral intake. To compare the efficacy of slow-release VPA to that of LD in a double-blind fashion, we chose the slow-release form of LD. Though the efficacy of LD in

RLS has been demonstrated previously [9], the efficacy of slow-release LD monotherapy has not been adequately investigated so far. It may be a source of bias that different treatment sequences were not separated by wash-out periods. However, outcome variables were measured at the end of each treatment sequence, when (based on the half lives of the drugs) there was probably no effect of the drug taken before. Moreover, serum levels of VPA greater than zero were only demonstrated with VPA therapy. VPA and LD, both significantly reduced the time of RLS symptoms between 0:00 and 4:00, the time period with typically most RLS symptoms. Furthermore VPA reduced RLS intensity and time during a 24-h period with the most significant reduction between 0:00 and 8:00. In contrast to LD, VPA did not exert any significant influence on PLM or arousal values. Although LD decreased PLMS and PLMAI, it increased spontaneous arousals. This has been described by others previously [8]. Long term efficacy was better with VPA than LD. The efficacy of dopaminergics in RLS is well known, although there is increasing evidence for augmentation, or emergence of RLS symptoms before medication dosing in the evening especially with LD therapy [1]. Fig. 1 shows the time of RLS symptoms for 4-hour time periods during the night-and-day-cycle. Compared with placebo, RLS time is increased between 12:00 and 20:00 with LD; although this increase is not statistically significant, it suggests a trend towards augmentation with LD, which was not observed with VPA.

VPA improved sleep quality in patients with PLMS but no RLS complaints in an open-labeled trial [5]. We did not observe this effect in RLS patients. The reason for that might be that PLMS in RLS and pure PLMS without RLS are different entities or that standard VPA is more effective in consolidating sleep than slow-release VPA. The discrepancy between subjective relief of RLS symptoms and sleep parameters with VPA might be due to involvement of different neurotransmitter systems in clinical RLS symptoms and in sleep regulation mechanisms. Although the mechanism of action of slow-release VPA in RLS is yet unknown, it seems to be an effective treatment for RLS, perhaps in some circumstances even superior to slow-release LD. Our results are encouraging in spite of being based on exploratory statistical analyses, but dopaminergics [4] have, in general, shown better results, both on sleep and paresthesias in RLS. Therefore, we do not recommend VPA as a first-line treatment for RLS. However, VPA may be an effective alternative or adjunctive treatment for patients unable to tolerate dopaminergics, or suffering from augmentation.

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