Sleep Changes After 4 Consecutive Days of Venlafaxine Administration in Normal Volunteers

Rafael J. Salín-Pascual, M.D., Ph.D., Lourdes Galicia-Polo, and René Drucker-Colín, M.D., Ph.D.

Background: The purpose was to examine the effect of the antidepressant drug venlafaxine on sleep architecture and periodic leg movements of sleep (PLMS) in normal volunteers.

Method: Eight normal volunteers were studied under laboratory sleep conditions as follows: 1 acclimatization night, 1 baseline night, and 4 consecutive nights of venlafaxine p.o. administration (75 mg during the first 2 nights and 150 mg the last 2 nights).

Results: Venlafaxine increased both wake time and sleep stage I. Sleep stages II and III were reduced. REM sleep time was reduced after the first venlafaxine dose, and, by the fourth night, REM sleep was completely suppressed in all volunteers. Six of the eight volunteers showed PLMS at a frequency above 25 per hour.

Conclusion: Venlafaxine produces several sleep disturbances, which include abnormal leg movements.

(J Clin Psychiatry 1997;58;348–350)

Received Feb. 11, 1997; accepted June 3, 1997. From the Servicio de Investigación del Hospital Psiquiátrico Fray Bernardino Alvarez, Secretaria de Salud (Dr. Salín-Pascual), Departamento de Fisiología, Facultad de Medicina (all authors), and Departamento de Neurociencias, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México (Dr. Drucker-Colín), México City, México.

Supported by DGPA-UNAM grant IN-200895 (Dr. Salín-Pascual) FIIRESIN and Fideicomiso UNAM (Dr. Drucker-Colín).

Reprint requests to: Rafael J. Salín-Pascual, M.D., Ph.D., Departamento de Fisiología, Facultad de Medicina, UNAM, Apdo. Postal 70-250, México D.F. 04510, México.

Venlafaxine is a new antidepressant with a dual mechanism of action (inhibition of reuptake of both serotonin and norepinephrine). Unlike the tricyclic antidepressants, venlafaxine does not displace ligands from muscarinic cholinergic, α_1-adrenergic, β-adrenergic, dopamine, or histamine binding sites of rat brain membranes.[1]

Some studies give strong support for the efficacy and tolerability of venlafaxine as an antidepressant.[2–4] Among the side effects reported by some patients that use venlafaxine are insomnia and periodic leg movements of sleep (PLMS). Other antidepressants such as tricyclics, monoamine oxidase inhibitors, and serotonin selective reuptake inhibitors also reduce or suppress rapid eye movement (REM) sleep in both human volunteers and patients, and some antidepressants also produce PLMS.[5] In rats, venlafaxine has been reported to produce a dose-response suppression of REM sleep as well as an increase in wake time.[6]

The purpose of the present study was to determine the effects of repeated administration of venlafaxine on sleep architecture and PLMS in normal volunteers, since no such study has been previously reported.

METHOD

Eight normal volunteers participated in the study (mean ± SD age = 29.87 ± 8.9 years; five women and three men). After the procedure had been fully explained, written informed consent was obtained from all subjects. They were then subjected to a structured psychiatric examination (Structured Clinical Interview for DSM-III-R [SCID]),[7] as well as physical examinations and laboratory tests. All study participants were drug-free, without a history of medical, psychiatric, or sleep disorders.

Volunteers were studied during sleep by all-night polygraphic recordings of electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), and thermistor measurement (mouth and nose). Two bands around the thorax and abdomen and two leg electrodes were used for recording purposes. Subjects underwent the following procedures: 1 acclimatization night, 1 baseline night, and 4 continuous nights of venlafaxine administration. Venlafaxine was administered 1 hour after the sleep recordings began (usually around 2100 hours). The first 2 nights, each volunteer received 75 mg p.o. and the following 2 nights 150 mg p.o.

Sleep recordings were visually scored according to standard criteria[8] by sleep laboratory technicians who were blind to the design. Sleep onset was defined as the first epoch of 8 continuous minutes of sleep after lights-out; awake time was defined as the minutes awake after sleep onset; and REM sleep latency was defined as the time from sleep onset to the first two epochs of REM sleep greater than 1 minute. Variables reflecting sleep architecture included time in each sleep stage. PLMS were visually scored and expressed as number of movements per

Table 1. Sleep Architecture in Eight Normal Volunteers During Venlafaxine Treatment

	Baseline		Treatment Night 1st[a]		2nd[a]		3rd[b]		4th[b]	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Wake time (min)	29.43	18.4	116.68[c]	86.4	72.25[c]	37.0	75.56[c]	41.9	161.81[c]	65.3
Stage I (min)	26.31	9.2	114.12[c]	63.4	116.31[c]	48.0	151.12[c]	49.5	148.62[c]	40.4
Stage II (min)	212.00	26.9	140.81[c]	70.1	207.00	69.3	178.81	43.1	121.06[c]	57.3
Stage III (min)	35.18	9.9	18.81[c]	12.5	22.75[c]	16.6	18.62[c]	12.4	10.87[c]	10.6
Stage IV (min)	50.31	16.4	27.43	19.3	43.10	30.0	27.43	33.2	28.06	31.7
Stage REM (min)	125.37	32.9	25.5[c]	41.9	11.12[c]	10.5	10.75[c]	27.6	0.0[c]	0.0
REM frequency (times)	4.25	1.3	1.62[c]	1.9	1.12[c]	0.8	1.25[c]	2.4	0.0[c]	0.0
REM average (min)	31.0	9.1	8.1[c]	11.9	8.3[c]	8.7	2.15[c]	4.1	0.0[c]	0.0
Phase shift (times)	52.6	9.6	95.87	36.9	108.37[c]	27.4	129.87[c]	35.5	128.0[c]	40.4

[a]1st and 2nd nights = venlafaxine 75 mg each night.
[b]3rd and 4th nights = venlafaxine 150 mg each night.
[c]Student's t test for repeated measures: $p < .01$

hour. One-way analysis of variance (ANOVA) was performed for each sleep variable, and the Student's t test with Bonferroni's correction was performed as post hoc analysis.

RESULTS

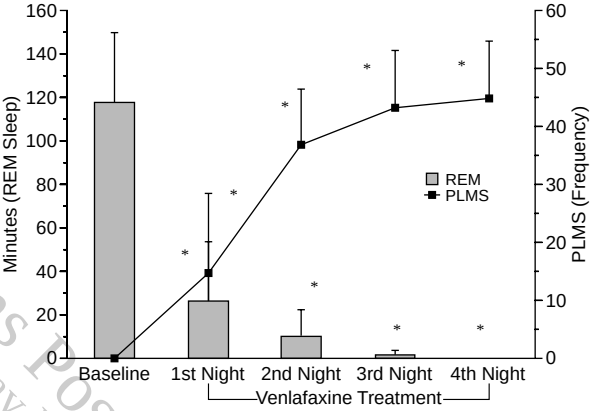
Table 1 shows sleep variables. Wake time ($F = 6.59$, $df = 4,35$; $p < .0007$) and sleep stage I ($F = 9.73$, $df = 4,35$; $p < .0001$) were increased during the 4 nights of venlafaxine administration. On the other hand, sleep stages II ($F = 4.12$, $df = 4,35$; $p < .007$) and III ($F = 3.95$, $df = 4,35$; $p < .009$) were reduced. REM sleep was dramatically reduced from the first night of venlafaxine treatment (reduction of 80% from baseline) to zero minutes by the fourth night in all volunteers ($F = 28.59$, $df = 4,35$; $p < .00001$). REM sleep reduction was due to a decrease both of REM sleep frequency ($F = 7.36$, $df = 4,35$; $p < .0004$) and of REM sleep average duration ($F = 18.86$, $df = 4,35$; $p < .00001$). Phase shifts of sleep-wake stages were increased from the first day of venlafaxine treatment to the end of the study ($F = 7.74$, $df = 4,35$; $p < .0003$).

Figure 1 shows the mean REM sleep time and mean frequency of PLMS during 8 hours of sleep for each of the 4 venlafaxine nights in six volunteers in which these leg movements were observed. They presented an index of PLMS above 25 movements per hour ($F = 8.54$, $df = 4,25$; $p < .0001$). Two of them also reported restless legs syndrome, which continued approximately a week after venlafaxine was withdrawn. Nausea, somnolence, and headache were also reported as mild side effects during the 4 days of venlafaxine administration in four of the eight volunteers. No correlation was found between REM sleep suppression and PLMS or between any of the side effects reported.

DISCUSSION

Our main findings were that venlafaxine suppressed REM sleep and reduced sleep stages 2 and 3. Also, 75% of the volunteers developed PLMS, and, of these, two also had restless legs syndrome. The primary limitation of the present study was the absence of an equivalent series of placebo nights against which to compare the effects of venlafaxine. Yet, the comparison of baseline variables with drug-night variables shows such a dramatic change that it is difficult to imagine the effect on these variables would be due to laboratory effects.

Figure 1. Significant Reduction of REM Sleep in Six Venlafaxine-Treated Subjects Accompanied by Increased PLMS Index (Mean PLMS Per Hour)†



†REM sleep expressed as mean ± SD. Abbreviation: PLMS = periodic leg movements of sleep.
*$p < .001$, Student's t test for repeated measures.

The effects of venlafaxine on the sleep-wake cycle appeared instantly after the first dose of 75 mg. One possible explanation for this finding is that the sudden increase in the availability of serotonin, norepinephrine, and dopamine (suggested to occur as a result of the administration of venlafaxine) may suppress REM sleep.[1] Pharmacologic manipulation of these neurotransmitters has been shown to reduce or even suppress REM sleep, while also promoting an increase in wake time.[9,10] The results of our study suggest an additive effect of repeated venlafaxine administration on the sleep variables. Since

the combined half-life of venlafaxine and its active metabolite O-desmethylvenlafaxine is about 12 hours,[3] it can be speculated that repeated doses every 24 hours induced an around-the-clock synaptic effect. It is precisely this REM sleep suppression effect, perhaps along with its main effects on serotonin and norepinephrine, that may contribute to its antidepressant effect.[11]

An interesting observation is venlafaxine's effect on PLMS and restless legs syndrome, which, although verbally reported by some patients, was recorded in the present study with high frequency and intensity. The physiopathology of PLMS and restless legs syndrome is unknown, although dopamine deficiency has been postulated.[12] Other antidepressants, as well as lithium,[5,13] have also been reported to be able to produce these movement abnormalities. In any case, venlafaxine could be used as a model for studying the physiopathology of these disorders.

Drug name: venlafaxine (Effexor).

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