Psychopharmacology (1997) 129:295–296

RAPID COMMUNICATION

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Effects of venlafaxine in the sleep architecture of rats

Received: 31 July 1996 / Final version: 5 November 1996

Abstract Different venlafaxine doses (1, 5, and 10 mg/kg) and saline solution were administered to ten male Wistar rats (Latin-Square design). Compared with saline, venlafaxine produced a dose-related supression of REM sleep and an increase in wake time while slow wave sleep was reduced. This effect is similar to the one that has been reported with some tricyclic antidepressants.

Key words Venlafaxine · REM sleep · Antidepressants

Introduction

Venlafaxine is a structurally novel phenylethylamine antidepressant. This drug inhibits the reuptake of serotonin, norepinephrine, and to a lesser extent, dopamine (Mendlewicz 1995). In animal models, it does not significantly inhibit muscarinic, histaminic, or adrenergic receptors and does not inhibit monoamine oxidase (Danjou and Hackett 1995). Trycyclic antidepressants (TAD) like imipramine or clomipramine produce significant suppressions of rapid eye movement (REM) sleep (Vogel et al. 1990; Buysee et al. 1995). Because REM sleep mechanisms are related to acetylcholine (Gillin et al. 1993), the anticholinergic effects of some of the TAD may contribute to the suppression of REM sleep.

The goal of the present study was to determine the effect of venlafaxine on sleep in the rat with one single administration of three different doses of this drug.

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Materials and methods

Ten male Wistar rats (200–300 g) were prepared for standard sleep-wake recordings, under deep pentobarbital anesthesia. EEG electrodes were implanted bilaterally over the frontal, parietal and occipital cortex. Electromyogram electrodes were threaded through the nucal muscles. One week after the surgery, the animals were assigned randomly (Latin-Square design) to the following manipulations: saline and venlafaxine 1, 5 or 10 mg (PO). At least 72 h was allowed between each test. Animals received the drug at 1000 hours and were then studied polysomnographically for 4 h. Animals were habituated to the recording environment for 2 days before the baseline recordings. Sleep recordings were scored blindly to the order of the drug administration. A one-way analysis of variance and Student *t*-test for repeated measures (with Bonferroni's correction) were performed as a post-hoc test.

Results

Table 1 shows the sleep architecture. Wake time was enhanced and slow wave sleep (SWS) was reduced at the highest venlafaxine dose (F = 6.9, df = 3,36, P<0.002,

Table 1 Sleep architecture in rats with venlafaxine

	Saline	1 mg	5 mg	10 mg
Wake (min)	77.7±18.5	84.29±20.7	74.5±20.0	117.7±13.81*
SWS (min)	149.7±19.9	148.1±20.7	157.2±20.4	119.2±13.4*
REMS (min)	13.3±4.3	7.7±2.7*	8.7±3.9*	3.5±1.5*
REMS lat (min)	80.71±28.0	117.17±46.6*	123.2±27.7*	160.05±16.2*
REMS freq.	9.5±1.76	4.8±1.6*	3.5±1.04*	2.6±0.81*
REMS avrg	1.37±0.26	1.69±0.58	2.44±0.58*	1.37±0.45

Student's "t" test for repeated measures (* P< 0.01)
Each situation was compared with saline
Data are means ±SD each group with ten animals
REMS avrg = REM sleep episodes average
REM freq. = number of REM sleep episodes

wake time and $F = 4.72$, $df = 3,36$, $P<0.01$, SWS), while REM sleep time was reduced dose-dependently after the three venlafaxine doses ($F = 8.91$, $df = 8,91$, $P<0.0008$). REM sleep latency was prolonged with significance at 1, 5 and 10 mg ($F = 6.32$, $df = 3,36$, $P<0.003$). REM sleep suppression effect was related to the number of REM sleep episodes, which were also reduced by venlafaxine ($F = 30.03$, $df = 3,36$, $P<0.00001$). As a result, a slight increase in the average duration of REM sleep episodes was observed ($F = 0.0041$, $df = 3,36$, $P<0.004$).

Discussion

Venlafaxine had a dose-response reduction in REM sleep time and an increase in REM sleep latency. Reduction in REM sleep time was due to a decrease in REM sleep episodes. SWS and Wake time changes were observed only at 10 mg.

REM sleep reduction may be related to greater availability of both serotonin and norepinephrine which has been the proposed mechanism of action for venlafaxine (Mendlewicz 1995). Pharmacological activation of both neurotransmitter systems has been reported to suppress REM sleep (Adrien 1995; Wauquier 1995). One important aspect in the results of the present study was that after a single administration of the drug a significant effect was obtained, which may say something about the potency of venlafaxine. This rapid effect was also observed when the effect of venlafaxine was evaluated on beta-adrenergic receptors in the pineal gland, where a single dose diminished the sensitivity of these receptors (Holliday and Benfield 1995). This last finding has been proposed as evidence of a shorter latency toward an antidepressant effect that this drug may have, relative to TAD.

The first two venlafaxine doses are in the range of the clinical recommended dosage. Hence, some patients with this dosage may have REM sleep suppression without sleep disruption. In fact, in depressed patients, Minot et al. (1992) reported a non-sedative effect with venlafaxine 75 mg (t.i.d.) as well as a REM sleep suppression effect. Long term administration of venlafaxine may give us some idea about tolerance effects for REM sleep suppression. Alternatively, venlafaxine may be useful in some sleep problems as narcolepsy, in which central nervous system stimulants and TAD have been used (Fritsch Montero et al. 1995).

Acknowledgement This study was supported by a grant DGAPA-UNAM IN-200895 to R.J.S-P.

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