Influence of Biperiden and Bornaprine on Sleep in Healthy Subjects

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Biperiden, 4 mg, an anticholinergic drug that is relatively selective for the M1 receptor subtype, and bornaprine, 4 mg, a nonselective M1 and M2 antagonist, were administered orally in a randomized, double-blind design to twelve healthy volunteers to investigate the effect on polysomnographically recorded sleep. Both drugs suppressed rapid eye movement (REM) sleep as reflected by an increase of REM latency and a decrease in the percentage of REM sleep period time with the effects of biperiden being more pronounced. No significant effect on slow wave sleep was observed. The results of this study support the hypothesis that both the M1 and the M2 receptor subtype are involved in the regulation of REM sleep in humans. ***[Neuropsychopharmacology 11:29–32, 1994]***

KEY WORDS: *Bornaprine; Biperiden; Cholinergic system; REM sleep; Slow wave sleep*

There is strong evidence that the cholinergic system is involved in the generation of rapid eye movement (REM) sleep (Hobson et al. 1986). Whereas the triggering of REM sleep by cholinergic neurons has been demonstrated convincingly (Hobson et al. 1975, 1986; Shiromani et al. 1987), it is still a question as to the extent muscarinic M1 and/or M2 receptors are involved in REM sleep regulation. Results of a recent study based on the microinjection of cholinomimetic drugs at the medial pontine-reticular formation in cats suggest that physiological and cholinergically induced REM sleep is mediated primarily by the M2 subtype of muscarinic receptors (Velazquez-Moctezuma et al. 1989, 1990). In comparison, biperiden, a preferential M1 antagonist, increased REM sleep latency, and reduced REM sleep time in healthy volunteers (Gillin et al. 1991; Salin-Pascual et al. 1991, 1993).

The aim of the present study was to investigate the effect of biperiden and bornaprine, two cholinergic antagonists, on sleep, especially REM sleep, in healthy subjects. The pharmacokinetic properties of both drugs are similar (Hollmann et al. 1984; Grimaldi et al. 1986; Mayo et al. 1980). Biperiden is considered to be a highly selective M1 antagonist (Burke 1986; Syvälahti et al. 1988; Eltze and Figala 1988; Freedman et al., 1988) with a M1 selectivity similar to that of pirenzepine (Syvälahti et al. 1987; Avissar and Schreiber 1989; Larson et al. 1991). Bornaprine, another centrally acting anticholinergic drug, lacks selectivity for the M1 or M2 receptor having equal affinity to both receptor subtypes (Kreiskott and Kretschmar 1985). The antagonism of bornaprine at the M2 muscarinic receptor has been demonstrated (Hufford et al., 1991). If M2 receptors are mainly responsible for the generation of REM sleep, a nonselective anticholinergic drug like bornaprine, that also shows M2 antagonistic properties, should have stronger REM sleep-suppressing effects compared to a preferential M1 receptor antagonist like biperiden.

SUBJECTS AND METHODS

We investigated 12 healthy volunteers with a mean age (±SD) of 25.01 ± 1.9 years (range 22–28 years) who

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were paid for their services. After one adaptation night, the subjects slept on night 2, night 5, and night 8 in the sleep laboratory. Biperiden, 4 mg, bornaprine, 4 mg, or placebo were given at 9 P.M. (i.e., two hours before the lights were turned off) on nights 2, 5, and 8 in a double-blind, randomized way. No sleep EEG recordings were performed in the drug-free nights of 3, 4, 6, and 7, which served to avoid carryover effects of the drugs given on the succeeding nights. Sleep was recorded between 11.00 P.M. and 7.00 A.M. according to standard procedures (Rechtschaffen and Kales 1968).

For descriptive purposes, mean ± SD were calculated. To compare placebo and drug conditions, a one-way ANOVA for repeated measurements was computed (*df* corrected according to the method of Greenhouse-Geisser). For ANOVAs yielding a p value $< .05$, statistical contrasts (two-tailed t-tests) were calculated to compare the three different conditions (placebo, bornaprine, biperiden) with each other.

RESULTS

In the ANOVA, no statistically significant effects concerning *sleep continuity* and *sleep architecture* occurred. Especially slow wave sleep (SWS) remained unchanged. Mean ± SD of *REM sleep variables* and the results of the statistical analysis are depicted in Table 1.

Concerning a lenient definition of REM latency (i.e., time from sleep onset to the first epoch of stage REM), no statistically significant effect as calculated by ANOVA occurred. With a strict definition of REM latency (i.e., calculating the interval from the first consecutive 10 min of uninterrupted sleep [at least stage 2] to the first REM period, which was at least 3 min in length), a significant effect was detected. Calculations of statistical contrasts revealed that bornaprine almost significantly increased REM latency, whereas with biperiden, a significant increase of REM latency was noted. Further statistically significant effects in the ANOVA occurred for REM percent sleep period time (SPT), and total REM density (%).

The calculation of contrasts demonstrated that all of these effects were stronger for biperiden, compared to placebo, than for bornaprine, compared to placebo. For REM percent SPT, a highly significant decrease was demonstrated for biperiden, whereas with bornaprine, the level of significance just reached $p < .05$. The duration of the first REM period was decreased significantly only with biperiden. With respect to phasic parameters of REM sleep, a significant increase of REM density of the whole night was noted with biperiden compared to placebo but not with bornaprine.

DISCUSSION

Biperiden, as well as bornaprine, suppressed REM sleep in healthy volunteers. Our results with biperiden are consistent with human pharmalogical (Salin-Pascual et al. 1991; Gillin et al. 1991) and with animal studies (Zoltoski et al. 1993), that demonstrated a dose-dependent suppression of REM sleep following the administration of biperiden. In accordance with animal data (Zoltoski

Table 1. Variables of REM Sleep (Mean ± SD) and Statistical Analysis

	ANOVA						*t*-Tests			
	Placebo	1	2	F	p		*df*	3	4	5
REM latency (lenient def.)	89.7 ± 40.7	126.8 ± 47.7	110.3 ± 43.7	1.65	.215		22 2			
REM latency (strict def.)	113.0 ± 51.8	158.8 ± 66.3	202.5 ± 86.2	5.29	.014	b	22 2	a	b	
REM % SPT	24.3 ± 6.3	19.2 ± 6.4	17.3 ± 4.0	8.29	.002	c	22 2	b	c	
Duration 1st REM period (min)	19.0 ± 10.8	15.8 ± 12.8	7.2 ± 8.8	3.49	.057	a	22 2		c	
Density 1st REM period (%)	15.1 ± 6.4	16.9 ± 9.0	19.6 ± 14.2	0.67	.519		22 2			
REM density (%) total	21.5 ± 7.5	24.7 ± 8.0	29.6 ± 6.6	5.06	.022	b	22 2		b	

Drug(s): 1 = bornaprine, 2 = biperiden, 3 = placebo versus bornaprine, 4 = placebo versus biperiden, 5 = bornaprine versus biperiden.
[a] $p < .1$.
[b] $p < .05$.
[c] $p < .01$.

et al. 1993), no increase of SWS could be found under biperiden.

The main hypothesis to test was if M1 and/or M2 receptors are involved in the regulation of REM sleep in humans. If M2 receptors are responsible for triggering REM sleep, as proposed by Velazquez-Moctezuma et al. (1989, 1990) based on animal data, the nonselective M1 and M2 antagonist bornaprine was supposed to have a stronger REM sleep-suppressing effect compared with the selective M1 antagonist biperiden. In contrast to this assumption, the M1 antagonist biperiden showed a stronger REM sleep-suppressing effect compared with the nonselective cholinergic antagonist bornaprine. Several explanatory factors should be considered.

First, although biperiden is a highly selective M1 antagonist comparable to pirenzepine (Syvälahti et al. 1987; Avissar and Schreiber 1989), the drug also has weak antagonistic effects on the M2 receptor. Thus, the possibility cannot totally be eliminated that at higher doses, biperiden may act also on the M2 receptor. Nevertheless, 4 mg of biperiden appear to be a low dose and the REM sleep-supressing effect of the nonselective M1/M2 antagonist bornaprine was lower. Restricting speculations, comparative studies in animals on the central nervous effect of both drugs are lacking, and we are not aware if both drugs have comparable central nervous activity at the same dose of 4 mg.

Second, as pointed out by Zoltoski et al. (1993), the hypothesis that REM sleep was triggered by M2 muscarinic receptors arose from studies in which relatively selective muscarinic agonists and antagonists were applied to the medial pontine reticular formation (Hobson et al. 1986; Shiromani et al. 1987). Thus, it might be that other anatomical sites, including those with M1 receptors, can modify or modulate the onset, maintenance, or nature of REM sleep (Zoltoski et al. 1993).

To summarize, our study confirms earlier results indicating that antimuscarinic agents suppress REM sleep and increase REM latency. The data, together with the other reported studies, suggest that M1 receptors may also be involved in the regulation of REM sleep in humans. Further studies are needed to clarify the exact functional and anatomical relationship between M1 and M2 receptors in the regulation of REM sleep.

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