ORIGINAL ARTICLE

The Effect of Donepezil on Sleep in Patients With Alzheimer's Disease: An Open Pilot Study

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Previous research has shown that acetylcholinesterase inhibitors may enhance REM sleep. The present pilot study indicates that donepezil also exerts a marked effect on REM sleep parameters in patients with Alzheimer's disease: REM density and duration of the first REM period were increased whereas REM latency was reduced. It will be interesting to study whether the donepezil effect on REM sleep is predictive of the therapeutic efficiency of the drug. **(Sleep and Hypnosis 2005;7(2):47-51)**

Key words: Donepezil, REM sleep, Alzheimer's disease

INTRODUCTION

Donepezil, an acetylcholinesterase inhibitor, is used in the treatment of Alzheimer's disease (1,2). The investigation of the effect of donepezil on sleep physiology, especially REM sleep, may be of interest since several studies (3,4) have shown that first, the percentage of REM and REM density sleep is reduced in patients with Alzheimer's disease and, secondly, the amount of REM sleep might parallel memory performance in animals and healthy humans (5-7). These findings stand in agreement with the cholinergic deficit hypothesis of Alzheimer's disease since cholinergic mechanisms play a crucial role in REM sleep regulation (8). Also, cholinergic agents reduce REM latency to a greater degree in middle-aged adults as compared with younger ones (9-11).

In an open-labeled pilot study, Schredl et al. (12) found that donepezil increases REM sleep and REM density, accompanied by shortened REM latencies. The first study of the effect of donepezil on sleep parameters in patients' with Alzheimer's disease was published by Mizuno et al. (13). They found an increase in REM sleep after a treatment period of 6 weeks (administering 5 mg donepezil in the morning) in 12 patients with mild to moderate stages of Alzheimer's disease. However, the results have to be interpreted with caution since the authors did not carry out an extra night prior to the baseline and treatment nights to allow adaptation to the sleep laboratory setting. Especially the marked increase in sleep efficiency in parallel with an decrease in sleep latency from the first lab night to the second supports the hypothesis that the findings might be explained by the so-called first-

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night effect (reduced sleep efficiency together with reduced REM sleep percent, e.g., [12]). The present study was designed to study the effect of donepezil on sleep at the beginning and after three months treatment in patients with Alzheimer's disease.

METHODS

Participants

Four outpatients of our memory clinic with mild to moderate stages of Alzheimer's disease (1 woman, 3 men) participated in the study. Their mean age was 67.3±9.8 years, ranging from 54 to 76 years of age. The patients had given written informed consent and were not paid for their participation. The research protocol had been approved by the local ethics committee. One patient suffered from sleep apnea, which had been diagnosed ten years before, and was treated effectively with CPAP. CPAP pressure was constant during the course of the study.

Design

Overall, the subjects spent six nights in the sleep laboratory. Night 1 served as an adaptation night and included measures of nasal and oral airflow, chest and abdomen movements, blood oxygen saturation and anterior tibialis electromyogram in both legs. The second and third nights were considered the baseline nights. Prior to the fourth night, participants received 5 mg donepezil orally one hour before bedtime. After three months at home (continuing the medication of 5 mg donepezil prior to bedtime for one month, then three patients increased the dosage to 10 mg; one patient did not tolerate 10 mg due to side effects on the cardiac function and was kept on 5 mg), all participants returned for two additional nights in the sleep laboratory. Blood samples were taken after 3 months to determine serum levels of donepezil.

Sleep

Sleep was recorded between 23.00 hrs and 7.00 hrs by means of the following standard procedures: EEG (C3-A2, C4-A1), electrooculogram (EOG), submental electromyogram (EMG) and electrocardiogram (ECG). Sleep records were scored under blind conditions by applying the commonly used criteria of Rechtschaffen and Kales (14). The following sleep parameters were computed:

Sleep continuity: Measures were taken of sleep period time (SPT; time between sleep onset and final morning awakening), sleep efficiency (ratio of time in bed minus time awake to time in bed), sleep latency (time span from „lights off" to occurrence of first stage 2 or REM), and the number of awakenings of at least 0.5 minutes duration.

Sleep architecture: Stage 1, 2, slow-wave sleep (stage 3 and 4) and REM (expressed in percent of SPT) were measured.

REM sleep: REM latency is the time period between sleep onset and the first REM period of at least 3 minutes. In addition, a second measure was derived for REM latency by subtracting all epochs scored as "being awake". REM density is the ratio of 3-second miniepochs with eye movements to all 3-second epochs of REM sleep. This was done for the entire night as well as for the first REM period. In addition, the length of the first REM period and the number of REM periods were included in our analyses.

Statistical analysis

T-tests for dependent samples were carried out to analyze the differences between baseline nights and first donepezil night, baseline nights and last donepezil night. Since for REM sleep variables the direction of the effect was predicted, one-tailed tests were applied. All other sleep parameters were tested two-tailed. Statistical analyses were carried out with the SAS for Windows (Version 8.02) software package.

RESULTS

The serum levels of donepezil after three months treatment ranged from 35 to 45 ng/ml and were, thus, within the therapeutically common range. Three patients had moderate to severe indices of periodic limb movements during sleep ranging from 23.5 to 113.8 per hour without arousals and 1.9 to 11.2 per hour with arousal. One patient had a mild sleep apnea syndrome with a respiratory disturbance index of 16.4 apneas/hypopneas per hour.

Table 1 shows the sleep parameters of the adaptation, baseline, and donepezil nights. There were no marked negative effects of donepezil on sleep efficiency or sleep continuity. However, sleep efficiency was very low in this sample (a maximum of 60% in the last laboratory night) reflecting the sleep problems often reported in this patient group.

Regarding REM sleep parameters, the percentage of REM sleep was not altered by the administration of donepezil (see Table 2). The findings of shortened REM latency and increased REM density, however, indicate that the cholinergic system was stimulated. Whereas the effect on the duration of the first REM period and REM density remained quite stable over the treatment period of three months, the effect of shortening REM latency by the use of donepezil was not found in the last night.

Table 1. Sleep parameters of adaptation, baseline and donepezil nights (Means ± SD)

Variable	Adaptation Night	Baseline 1 Night	Baseline 2 Night	1. Donepezil Night	2.Donepezil Night (after 3 months)	3.Donepezil Night (after 3 months)	t-test[1] BL1 + 2 vs. 1. Donepezil		t-test[1] BL1 + 2 vs. 3. Donepezil	
Sleep efficiency (%)	48.2 ± 3.2	58.9 ± 16.6	57.9 ± 12.9	49.5 ± 12.6	47.2 ± 18.9	60.5 ± 9.1	-1.1	.3399	0.4	.7423
Sleep latency (min)	21.8 ± 11.0	22.4 ± 14.3	39.8 ± 53.8	34.0 ± 4.1	84.9 ± 72.7	40.8 ± 47.5	0.2	.8407	0.7	.5536
Number of awakenings	45.3 ± 31.9	39.0 ± 26.5	35.5 ± 24.8	39.5 ± 23.4	38.3 ± 12.5	43.0 ± 23.7	0.3	.8088	1.7	.1829
Time awake (% SPT)	36.9 ± 24.3	27.5 ± 20.5	28.4 ± 15.4	41.0 ± 16.0	44.7 ± 14.8	28.6 ± 2.8	1.9	.1577	0.1	.9426
Stage NREM 1 (% SPT)	29.5 ± 10.4	31.9 ± 12.4	30.9 ± 3.0	25.9 ± 9.7	24.3 ± 15.3	27.3 ± 14.5	-1.0	.4104	-0.7	.5499
Stage NREM 2 (% SPT)	25.7 ± 15.4	29.8 ± 14.4	23.8 ± 11.9	20.0 ± 6.6	18.9 ± 12.0	27.2 ± 16.4	-1.6	.2029	0.1	.9625
Slow-wave sleep (% SPT)	0.4 ± 0.7	0.3 ± 0.4	0.1 ± 0.2	0.0 ± 0.1	0.1 ± 0.2	0.0 ± 0.1	-1.9	.1474	-1.9	.1474

[1]probability values are two-tailed

Table 2. REM sleep parameters of adaptation, baseline and donepezil nights (Means ± SD)

Variable	Adaptation Night	Baseline 1 Night	Baseline 2 Night	1. Donepezil Night	2.Donepezil Night (after 3 months)	3.Donepezil Night (after 3 months)	t-test[1] BL1 + 2 vs. 1. Donepezil		t-test[1] BL1 + 2 vs. 3. Donepezil	
Stage REM (% SPT)	7.5 ± 4.3	10.4 ± 4.3	16.7 ± 10.4	13.1 ± 7.5	11.5 ± 7.5	16.2 ± 3.8	-0.6	.6982	0.9	.2199
REM latency (min.)	152.2 ± 113.4	38.8 ± 8.4	53.9 ± 34.1	32.6 ± 11.9	97.6 ± 74.7	58.3 ± 3.2	-1.1	.1824	1.4	.8744
REM latency (3 min REM)	171.4 ± 135.4	101.8 ± 88.9	74.0 ± 45.3	35.9 ± 19.5	98.0 ± 75.4	59.4 ± 1.8	-2.3	.0524	-0.9	.2146
Duration (1. REM period)	12.5 ± 9.5	9.6 ± 4.5	13.8 ± 9.7	14.3 ± 8.3	22.4 ± 21.4	26.9 ± 14.4	1.2	.1601	2.7	.0359
REM density (1. REMP)	28.6 ± 15.4	20.1 ± 6.8	19.4 ± 3.6	36.7 ± 14.3	30.3 ± 17.2	36.5 ± 19.8	2.4	.0488	1.6	.1094
REM density (total night)	31.2 ± 13.3	24.7 ± 11.5	22.6 ± 7.4	30.9 ± 14.9	34.1 ± 12.2	30.6 ± 10.8	1.2	.1599	2.1	.0633

[1]probability values are one-tailed

DISCUSSION

During the present study, donepezil was generally well tolerated, and a negative effect on sleep efficiency and sleep latency as reported for other acetylcholinesterase inhibitors such as galanthaminehydrobromide (15) or tacrine (16) was not observed. A possible impairment in slow-wave sleep in association with donepezil

which was found for galanthaminehydrobromide (15) or RS 86 (17), could not be examined since slow-wave sleep was scarcely present, a well-known characteristic of advanced age (3).

As expected and despite the small sample size, a single dose of donepezil had a considerable effect on REM sleep parameters such as REM density and the duration of the first REM period as well as a reduction of REM latency. The results, however, must be considered preliminary since the design of the study was not double-blind placebo controlled.

The finding that REM latency reduction was less prominent in the donepezil night after three months than in the first night might reflect counter-regulatory processes. However, one should keep in mind that the percentage of REM sleep and REM density were still elevated. Since these REM sleep parameters are reduced in patients with Alzheimer's disease (3), it would be most interesting to examine whether a long-term treatment with acetylcholinesterase inhibitors in these patients will increase the percentage of REM sleep and REM density to the levels of healthy controls.

Overall, the patients' sleep efficiency was reduced reflecting the sleep problems often reported in this patient group (18). Whether the syndrome of periodic limb movements during sleep are more prominent in these patients than in healthy, elderly persons is difficult to evaluate due to the small sample size but it seems worthwhile to investigate the prevalence of this disorder because it might contribute considerably to the sleep problems of these patients. A marked first-night effect could be observed in this patient group, especially for REM percentage and REM latency, so that the findings of Mizuno et al. (13) have to be considered as preliminary. Double-blind, placebo-controlled studies are necessary to corroborate the findings of these pilot studies.

Mizuno et al. (13) reported a positive correlation between improvement in cognitive functioning and increase REM sleep percentage, both measured after 6 weeks donepezil treatment. I.e., the amount of REM sleep is a marker of cognitive functioning in these patients. It will be very interesting to study this relationship in a larger patient sample. In a similar way, Schredl et al. (12) found a significant correlation of the improvement of an implicit learning task from evening to morning with the amount of REM sleep enhanced by donepezil in elderly, healthy persons. Another interesting idea is the question as to whether the effect of the first administration of donepezil on sleep (intensifying REM sleep and, thus, reflecting the cholinergic potency) is predictive of the treatment efficiency of this drug.

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