PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY, 2018
VOL. 28, NO. 1, 14–18
https://doi.org/10.1080/24750573.2017.1368856

Taylor & Francis
Taylor & Francis Group

The effect of cholinesterase inhibitors on sleep in the patients with Alzheimer's disease: an observational prospective study

Osman Korucu[a], Bekir Enes Demiryürek[b], Gülin Morkavuk[c] and Aysu Akbaş Korucu[d]

[a]Neurology Department, Kecioren Training and Research Hospital, University of Health Sciences, Ankara, Turkey; [b]Neurology Department, Sakarya Education and Research Hospital, University of Health Sciences, Ankara, Turkey; [c]Neurology Department, Ufuk University Hospital, Ankara, Turkey; [d]Turkish Drug & Medical Device Institution, Ankara, Turkey

ABSTRACT

INTRODUCTION: The aim of this study was to evaluate the essential effects of cholinesterase inhibitors between the first days of the medication and after 1 month in the patients have not the history of disease, the patients not used the medicines which effect the sleep or the patients started new medication.

METHODS: Patients diagnosed with mild to moderate stage Alzheimer's disease according to DSM-IV criteria (age: 55–85) were admitted in this multi-centred study between December 2014 and January 2017. Thirty five patients with mini mental test score between 14 and 24 were included in the study. Pittsburgh Sleep Quality Index (PSQI), Cornell Scale for Depression in Dementia (CSDD), Beck Anxiety Scale (BAS) and Standardized Mini Mental Test (SMMT) were given to all patients were used in first days of treatment and at least after 1 month.

RESULTS: Twenty patients (57%) were using Donepezil and 15 patients (43%) were using Rivastigmine. Gender, marital status, educational status and family history of dementia were not statistically significant difference for both of the groups. There was no statistically significant difference between the first and second evaluation for two treatment groups in SMMT, CSDD and BAS scores (p values .748, .232 and .611, respectively). In both groups, positive effect were observed in PSQI scores after 1 month of treatment, but this positive effect was not found to be statistically significant (p: .558).

DISCUSSION: When donepezil and rivastigmine were compared in this study, it was observed that they had similar positive effects on sleeping quality, but there was not statistically significant difference.

ARTICLE HISTORY
Received 22 May 2017
Accepted 14 August 2017

KEYWORDS
Alzheimer; sleep; donepezil; rivastigmine; dementia; Pittsburgh

Introduction

As well as social problems associated with forgetfulness, sleep disorder can also create serious problems for the patients with Alzheimer's disease (AD) and their relatives. Sleep disorder is observed in 40% of dementia patients [1,2]. Several studies showed that sleep disorder was observed more often in advancing stages of dementia and sleeping disorder showed a linear correlation with the intensity of the disease [3]. AD patients may experience insomnia symptoms such as REM sleep behaviour disorder, sleeping difficulty, intermittent sleeping, early morning awakening, and sleep apnoea or excessive daytime sleepiness which emerges as a result of insomnia. These sleep disorders are important as risk factors in the development of psychiatric symptoms as well as their effects on life quality, functional and cognitive capabilities [4]. All these factors increase the burden on the caregiver. Acetylcholine has an active role in regulating normal sleep patency and strengthening the memory [5]. Cholinesterase inhibitors used in AD patients contribute to clinical improvement by providing natural circadian rhythm of central cholinergic conduction [6]. The majority of acetylcholine is released in REM sleep. According to previous studies, cholinesterase inhibitors have been reported to increase the amount of acetylcholine by prolonging the REM sleep period and consequently they caused sleep disorders [7–9]. Cholinesterase inhibitors used in AD treatment today are rivastigmine, donepezil and galantamine. There are studies in the literature that examine the effects of donepezil, rivastigmine and galantamine on sleeping behaviour. These studies have reported that donepezil disrupts sleep quality, rivastigmine has a negative effect and galantamine has no effect on sleep quality [8,11–13]. However, in these studies, the population of the patients are seen to use the medicines affecting sleep.

In our study, the effect of cholinesterase inhibitor drugs on sleep behaviour, in addition to depression and anxiety symptoms, were investigated and drug effect on sleep quality was observed. Our aim in the present study was to investigate the effect of the cholinesterase inhibitors by excluding the medicines and

CONTACT Osman Korucu osmankorucu2@gmail.com, tubersulf@yahoo.com Kecioren Egitim ve Arastirma Hastanesi, Pınarbaşı Mah. Sanatoryum Cad. Ardahan Sok. No:25, 06380 Kecioren, Ankara, Turkey

disease which have the known influence on sleep, and additionally, to observe the only effect of the medication on sleep quality interrogating depression and anxiety disrupting the sleep quality.

Methods

This prospective observational medication study was conducted at second- and third-level hospitals between December 2014 and January 2017. The study protocol was approved by the local ethics committee. This study was registered as a Turkish Ministry of Health drug and pharmacy trial (number 2014-PMS-66). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patients who were started the medicines a few days ago and the patients admitted again with any reason were invited to study. Informed consent forms were obtained from all patients and/or their relatives.

Patients treated and diagnosed with mild to moderate stage AD according to DSM-IV criteria (age: 55–85), and patients who were at least literate with mini mental score between 14 and 24 were included in this multi-centred study.

Patients, who used antipsychotic, antidepressant, sedative, opioid, benzodiazepine derivative drugs and who have another accompanying neurodegenerative disease, cerebrovascular disease history, mild cognitive impairment (MCI) diagnosis and another significant neurological, psychiatric disease or medical condition that may affect sleep quality, were excluded from the study. Age, gender, marital status, education level, family history of dementia, comorbid diseases, medications and cholinesterase inhibitor use of patients were recorded in case report form. Beck Anxiety Scale (BAS), Cornell Scale for Depression in Dementia (CSDD), Standardized Mini Mental Test (SMMT) and Pittsburgh Sleep Quality Index (PSQI) surveys were administered on the first days of treatment, and at least 1 month later, to the patients with AD, whose treatment had already been started. Patients used the drugs belonging to exclusion criteria between two evaluation, patients had the any diseases causing exclusion, and the patients did not admit to second test 1 month later were excluded.

Statistical analysis

Descriptive statistics of the categorical variables included in the study were given by frequency, and statistics which vary with the percentage were given by mean, standard deviation, median, minimum and maximum values. Conformity of continuous variables with normal distribution was evaluated by Shapiro–Wilk test. Mann–Whitney *U* test was used for comparison of two groups of variables which do not exhibit normal distribution, whereas, independent *t* test was used for comparison of two groups of variables which exhibit normal distribution. Wilcoxon test was used for in-group comparison of variables which do not exhibit normal distribution, whereas, *t* test was used for in-group comparison of variables which exhibit normal distribution. Among from all statistical analyses in the study, comparisons which are below 0.05 were considered statistically meaningful.

Results

Fifty eight patients were evaluated for the study. Five women and one man patients were not included in the study because they used cholinesterase inhibitors along with antidepressants. Remaining six patients did not come to first control in a month. Eleven patients were excluded because eight of them started to use antipsychotics and the other three patients began to take antidepressants between two evaluations (Figure 1).

Seventeen (49%) women, and 18 (51%) male patients finished the study. Twenty patients (57%) were using donepezil and 15 patients (%43) were using rivastigmine. There were no patients using galantamine. The patients were receiving donepezil tablet in the morning. After being included in the study, none of the patients used memantine, or medications which are known to affect sleep quality, during the first 1 month period. The mean age of the donepezil group was 73.50 ± 6.66, and 73.93 ± 7.62 in the rivastigmine group. During second evaluation of the patients, one patient was treated with 4.6 mg and 14 patients were treated with 9.5 mg rivastigmine; among the patients who received donepezil, 17 patients received 10 mg, 3 patients received 5 mg per day. Gender, marital status, educational status and family history of dementia were not statistically significant for both of the groups (Table 1).

There was no statistically significant difference between the first and second evaluation between the two treatment groups in SMMT, CSDD and BAS scores (*p* values .748, .232 and .611, respectively). CSDD scores in the group of rivastigmine were higher in first evaluation; however, there were not any differences in terms of score change comparing to donepezil group. In both groups, a positive effect was observed with PSQI after 1 month of treatment, but this positive effect was not found to be statistically significant (*p*: .558) (Table 2). PSQI scores 5 and above are regarded as poor sleep quality. After using cholinesterase inhibitors, a significant decrease in PSQI scores (mean ± SD) were detected (Table 2); however, this reducing did not take the patients except one to the level of good sleep quality at following period (Table 3).

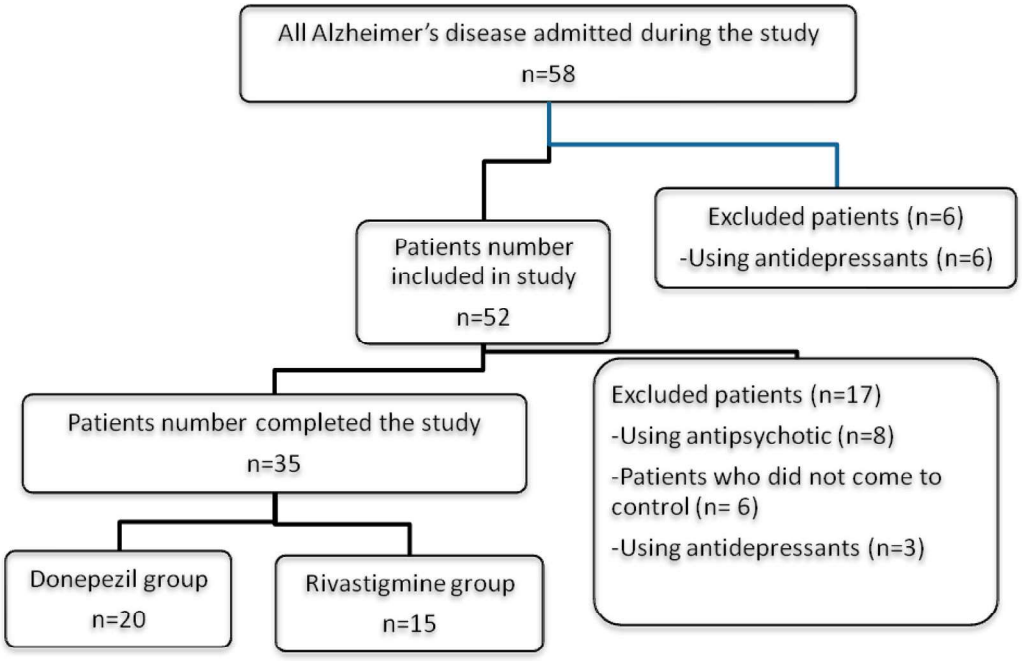

Figure 1. Patient flow chart.

Table 1. Sociodemographic characteristics and family history of patients based on type of medication.

		Donepezil (*n*:20)	Rivastigmine (*n*:15)	*p*
Sex	Female	10 (%50)	7 (%47)	
	Male	10 (%50)	8 (%53)	.845
Marital status	Married	15	7	
	Single	5	8	.086
Educational status	Literate	12 (%60)	8 (%53)	
	Primary school	8 (%40)	5 (%33)	.342
	High school	–	2 (%14)	
Dementia in family	Positive	6	8	
	Negative	14	7	.163

BAS score applied to patients suggests: 0–9 normal anxiety, 10–18 mild anxiety, 19–29 moderate anxiety and 30–63 severe anxiety. The CSDD score of 8 and above suggests depression. The clinical significance and *p* values of depression, anxiety and sleep quality changes of patients are given in Table 3.

Discussion

Sleep disorders frequently accompany AD and impair the patients' quality of life. In our study, we intended to detect the exact influence of cholinesterase inhibitors on sleep quality, which are frequently used in patients with AD. AD patients are frequently treated with medications that influence quality of sleep negatively, due to behavioural and psychiatric symptoms. Hence, by means of exclusion criteria and timing of the tests, we aimed to isolate the effect of cholinesterase inhibitors on sleep quality at the beginning of the treatment and after at least one-month period.

Unlike previous studies, patients had a lot of factors that effect the sleep prior the study or in including period were excluded. None of the patients included in our study was using galantamine. Although we have found similar positive effects in both groups of the patients using donepezil and rivastigmine, on the scores of quality of sleep, the difference was not statistically significant. However, this positive finding is important for daily clinical practice. Although in previous studies, donepezil had negative effects on sleep, our study showed that its effect on sleep was similar in comparison with rivastigmine. Because the number of the patients in the group of rivastigmine had depression and poor sleep quality in first evaluation is higher than that of donezepil group and with the

Table 2. First and second SMMT, CSDD, BAS scores and PSQI values at least 1 month apart.

	Donepezil (*n*:20)		Rivastigmine (*n*:15)		Total (*n*:35)	
	Mean ± SD	Median (min – max)	Mean ± SD	Median (min – max)	Mean ± SD	Median (min – max)
SMMT 1	18.65 ± 2.92	18 (14–24)	20.06 ± 3.28	21 (14–24)	19.25 ± 3.11	19 (14–24)
SMMT 2	18.65 ± 3.29	18.5 (13–24)	20.4 ± 3.37	21 (15–26)	19.4 ± 3.39	20 (13–26)
CSDD 1	7.6 ± 4.71	7 (0–20)	11.2 ± 6.33	11 (0–26)	9.14 ± 5.67	9 (0–26)
CSDD 2	7.5 ± 4.57	7.5 (0–20)	10.53 ± 5.93	10 (1–24)	8.8 ± 5.34	8 (0–24)
BAS score 1	9.5 ± 7.25	8.5 (2–29)	12.86 ± 6.02	14(4–26)	10.94 ± 6.86	10 (2–29)
BAS score 2	9 ± 7.12	8 (0–29)	12.93 ± 9.07	11 (4–40)	10.68 ± 8.13	10 (0–40)
PSQI 1	8.35 ± 5.45	8 (0–18)	9.07 ± 4.21	9 (2–17)	8.66 ± 4.9	9 (0–18)
PSQI 2	7.9 ± 4.93	9 (0–17)	8.73 ± 4.06	10 (2–16)	8.26 ± 4.53	9 (0–17)

SMMT: Standardized Mini Mental Test; CSDD: Cornell Scale for Depression in Dementia; BAS: Beck Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index.

Table 3. The number of patients with normal and abnormal scores during two successive evaluations.

		Donepezil (*n*:20)	Rivastigmine (*n*:15)	*p*
CSDD 1–CSDD 2	Normal score	11–10	4–4	.094–.163
	Depression	9–10	11–11	
BAS 1–BAS 2	Normal score	10–10	3–5	.176–.788
	Mild anxiety	7–7	6–6	
	Moderate anxiety	2–2	5–3	
	Severe anxiety	1–1	1–1	
PSQI 1–PSQI 2	Good sleep quality	7–8	3–2	.331–.084
	Poor sleep quality	13–12	12–13	

CSDD: Cornell Scale for Depression in Dementia; BAS: Beck Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index.

reason of sample size, any statistically significant difference could not be seen between two groups. Nevertheless, even results of our study is not statistical, donepezil has positive effect on sleep clinically like rivastigmine. At first evaluation, 1 month later, both in two patients groups the decrease was seen in PSQI scores and this reduction shows a positive change in sleep quality. As far as we know, this is the very first study comparing the effects of rivastigmine and donepezil on sleep, including anxiety and depression scores as well.

Song et al. showed that intake of donepezil in the morning was preferable to evening, in order to prevent the negative effect of cholinesterase inhibitors on the quality of sleep [10]. In our study, as the patients took donepezil in morning, negative effects of it on sleep may not have been observed and a significant difference may not has been found in comparison with rivastigmine.

Effect of cholinesterase inhibitors using PSQI on sleep was investigated in a study conducted by Naharci et al. They found a superior decline in post-treatment PSQI score in patients using galantamine, although not statistically significant, in comparison with other groups of patients (donepezil, rivastigmine and controls) and they advised to use galantamine in dementia as a first-option medication [14]. In a randomized double-blind trial, donepezil and galantamine did not have deleterious effects on sleep, furthermore galantamine was found to be slightly more beneficial than of donepezil in terms of sleep quality [7]. In our study, although galantamine group was not investigated, we think that cholinesterase inhibitors may influence sleep positively. Another study found a positive effect of donepezil in only AD patients with obstructive sleep apnea [15], whereas another study found that donepezil raised apnea/hypopnea, desaturation and the lowest saturation indexes [16]. Another study showed that rivastigmine transdermal patch ameliorated the symptoms of sleep breathing disorders [17].

Sleeping disorders are important co-factors for the progression of psychiatric symptoms, as well as for quality of life, functional and cognitive skills of the patients [1,2,4].

In a previous study, sleep disorders of the dementia patients using memantine, donepezil, rivastigmine and galantamine were evaluated with CSDD. It was observed that the patients with sleep disorders had depressive symptoms; however, these four medications were not statistically superior to one another in any aspects [2]. In our study, patients in both medication groups were given CSDD and BAS tests and statistically significant differences were not found between first and second examination scores. Meanwhile, CSDD and BAS scores in rivastigmine group were higher, albeit non-significant. It is not clear whether sleep disorders are connected with AD, and co-incident depression, or whether secondary depressive symptoms arose due to sleep disorders. According to our observation, donepezil and rivastigmine have no negative effect on sleep by any means.

In a review article evaluating the relation between sleeping behaviour and AD, methods of sleeping behaviour were examined. It was stated that subjective sleep surveys (PSQI, sleep sickness survey and Athens insomnia scale) had limited value for AD patients with mild to moderate stage sleep disorders [18]. Therefore, new methods are needed, considering that both polysomnography and sleep surveys are not sufficient for AD patients to investigate sleep disorders. Wrist actigraphy is a method used to measure inactivity versus activity, or wakefulness versus sleep, over a period of 24 hours, which can be a reliable alternative. Wrist activity in dementia patients during sleep and wakefulness was evaluated by Ancoli-Israel et al.; a correlation between EEG recording and actigraphy was observed during total sleep and wakefulness, and this method was found to be highly sensitive and specific [19].

The present study has several limitations such as a short follow-up period, and sleep status was evaluated by the PSQI scale alone. Sleep quality of patients can be determined more clearly by polysomnography. However, AD patients may not be eligible for this type of examination. Other limitations of our study are: anxiety and depression were evaluated only by scales, and that mild to moderate stage AD patients were included in the study. In spite of above-mentioned limitations, the main superiority of our study compared to previous studies is that, our patients had no drug use and medical condition which are known to affect the sleep quality. It is widely accepted that sleep disorders correlate with the course of the illness. In advanced stage AD patients, sleep disorders may be more evident.

In conclusion, good sleep quality of AD patients is important for both patients and caregivers. The choice of medication in AD treatment may have additional

benefits in terms of quality of life and cognitive status of the patient. In many studies carried out before, it was stated that donepezil had adverse effects on sleeping quality. Yet, in this study when donepezil and rivastigmine were compared with each other, it was observed that they had similar positive effects on sleeping quality but there was not a significant statistical difference. We suggest that donepezil should be taken early in the morning. Thereby circadian rhythmicity would be preserved with the cholinergic treatment of AD, and sleeping disorders may be prevented. Further studies are needed to clarify the effect of AD medications on sleeping disorders.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Tractenbery RE, Singer CM, Cummings JL, et al. The sleep disorders inventory: an instrument for studies of sleep disturbance in persons with Alzheimer's disease. J Sleep Res. 2003;12(4):331–337.
[2] Miu DKY, Szeto SSL. Sleep disturbances among a group of dementia participants. J Clin Gerontol Geriatrics. 2012;3:105–109.
[3] McCurry SM, Reynolds CF, Ancoli-Israel S, et al. Treatment of sleep disturbance in Alzheimer's disease. Sleep Med Rev. 2000;4(6):603–628.
[4] Sinforiani E, Terzaghi M, Pasotti C, et al. Hallucination and sleep-wake cycle in Alzheimer's disease: a questionnaire-based study in 218 patients. Neurol Sci. 2007;28(2):96–99.
[5] Bombois S, Derambure P, Pasquier F, et al. Sleep disorders in aging and dementia. J Nutr Health Aging. 2010;14(3):212–217.
[6] Nieoullon A, Bentue Ferrer D, Bordet R, et al. Importance of circardian rhythmicity in the cholinergic treatment of Alzheimer's disease: focus on galantamine. Curr Med Res Opin. 2008;24(12):3357–3367.
[7] Ancoli-Israel S, Amatniek J, Ascher S, et al. Effects of galantamine versus done pezil on sleep in patients with mild to moderate Alzheimer disease and their caregivers: a double-blind, head-to-head, randomized pilot study. Alzheimer Dis Assoc Disord. 2005;19(4):240–245.
[8] Cooke JR, Loredo JS, Liu L, et al. Acetylcholinesterase inhibitors and sleep architecture in patients with Alzheimer's disease. Drugs Aging. 2006;23(6):503–511.
[9] Moraes WS, Poyares DR, Guilleminault C, et al. The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: a double-blind placebo-controlled study. Sleep. 2006;29(2):199–205.
[10] Song HR, Woo YS, Wang HR, et al. Effect of the timing of acetylcholinesterase inhibitor ingestion on sleep. Int Clin Psychopharmacol. 2013;28(6):346–348.
[11] Naharcı I, Bozoglu E, Kocak N, et al. Analysis of the efficiencies of galantamine and donepezil on sleep disorder in patients with dementia. BULL CLIN PSYCHOPH. 2011;21(4):339–344.
[12] Chankrachang S, Senanarong V, Poungvarin N, et al. The effect of galantamine on sleep quality in Thai Alzheimer's disease patients. J Med Assoc Thai. 2008;91(9):1343–1349.
[13] Stahl SM, Markowitz JS, Papadopoulos G, et al. Examination of nighttime sleep-related problems during doubleblind, placebo-controlled trials of galantamine in patients with Alzheimer's disease. Curr Med Res Opin. 2004;20(4):517–524.
[14] Naharci MI, Ozturk A, Yasar H, et al. Galantamine improves sleep quality in patients with dementia. Acta Neurol Belg. 2015;115(4):563–568.
[15] Moraes W, Poyares D, Sukys-Claudino L, et al. Donepezil improves obstructive sleep apnea in Alzheimer disease: a double-blind, placebo-controlled study. Chest. 2008;133(3):677–683.
[16] Sukys-Claudino L, Moraes W, Guilleminault C, et al. Beneficial effect of donepezil on obstructive sleep apnea: a double-blind, placebo-controlled clinical trial. Sleep Med. 2012;13(3):290–296.
[17] Hyeyun K, Hyun JH. The effect of rivastigmine transdermal patch on sleep apne in patients with probable Alzheimer's disease. Dement Neurocogn Disord. 2016;15(4):153–158.
[18] Peter-Derex L, Yammine P, Bastuji H, et al. Sleep and Alzheimer's disease. Sleep Med Rev. 2015;19:29–38.
[19] Ancoli-Israel S, Clopton P, Klauber MR, et al. Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. Sleep. 1997;20(1):24–27.