INTRODUCTION

Sleep disturbance in patients with probable Alzheimer’s disease (AD) are frequent and disabling features, affecting approximately 25–60% of all patients. The most common sleep related complaints are insomnia, sleep fragmentation and excessive daytime sleepiness, frequently accompanied by sleep apnea in patients with probable AD.1 Change in sleep precedes the onset of cognitive symptoms in patients with AD, and a strong association exists between disrupted sleep and the development of AD.1 Cholinergic neuronal loss of Meynert nucleus in the basal forebrain is a pathophysiological hallmark of AD, and cholinergic activity in the central nervous system influences upper airway opening via the central and peripheral mechanism. Decreased thalamic pontine cholinergic projections may affect the respiratory drive, leading to both central and obstructive apnea in neurodegenerative diseases, including AD.2,4 The primary pharmacological treatments approved for AD are central acting cholinesterase inhibitors, and rivastigmine transdermal patches are frequently used in mild to moderate AD. The aim of this study was to evaluate the effects of rivastigmine transdermal patches on sleep architectures and sleep apnea in patients with probable AD.

METHODS

Patient population

Nineteen patients with probable mild to moderate Alzheimer’s disease were consecutively recruited from the neurocog-
pressive moods. After completing the questionnaire, the sub-
jects underwent two overnight polysomnographies (PSG), be-
fore and after rivastigmine transdermal patch application. PSG
recorded the electroencephalography (EEG), electrooculogra-
phy (EOG), chin electromyography (EMG), leg EMG, electro-
cardiography, and microphone for recording the sounds of sn-
oring, plethysmography for evaluating respiratory airflow and
effort, and oximetry for checking arterial oxygen saturation.
PSG was performed overnight in a sleep laboratory with a sleep
technologist in attendance. The scoring and staging followed
the American Academy of Sleep Medicine clinical guidelines.36
Hypopnea was defined ≥50% airflow reduction and ≥3%
desaturation or arousal. Sleep stages were based on 3 sources
of data coming from 7 channels: EEG, EOG, and chin EMG.
Sleep architecture considered the following variables: propor-
tion of non-rapid eye movement (REM) sleep period; N1,
N2, N3, and REM sleep periods from PSG data. Breathing
event during sleep was evaluated as the Apnea Hypopnea In-
dex (AHI) and Respiratory Disturbance Index (RDI), which
included AHI and respiratory event related arousal. Sleep dis-
ordered breathing (SDB) was defined by AHI or RDI of 5 or
higher, in association with excessive daytime somnolence. Oth-
er variables, including periodic limb movement during sleep
(PLMS), total sleep time (TST), total wake time (TWT), wake
time after sleep onset (WASO) and sleep onset latency (SL),
and sleep efficiency (SE), were calculated from data of over-
night PSG.

Neuropsychological tests

The K-MMSE was administrated at the screening, baseline
and at the end of the study. The clinical dementia rating (CDR)37
and Korean version of AD assessment scale-cognitive (ADAS-
cog) subscale12 were collected at the baseline and at end of
the study. All of the above neuropsychological tests were per-
formed with the same clinical psychologist for the entire pe-
riod of the clinical trial.

Statistical analysis

Sleep variables, such as the proportion of N1, N2, N3, and
REM, TST, TWT, WASO, SL, SE, RDI, AHI, PLMS index
from overnight PSG and ESS, SSS, BDI from the sleep ques-
tionnaire and K-MMSE, CDR ADAS-cog score were com-
pared with baseline and at 12 weeks after rivastigmine patch-
es were applied. Comparative analysis between the data from
the baseline study and the data from follow up studies for all
enrolled patients with AD were analyzed by the chi-square test
to compare categorical variables, and the paired t-test to com-
pare continuous variables, using SPSS v 17.0 software (SPSS
for Windows, SPSS Inc., Chicago, IL, USA).
RESULTS

Study population and disposition

Nineteen patients with probable AD with SDB were initially recruited in this study. Sleep and neurocognitive studies were performed at the baseline level for these nineteen patients with AD. After the baseline study, all enrolled patients were administered 5 cm² rivastigmine patch per day for 4 weeks. In the absence of any adverse events related with the patch, patients were treated to 10 cm² rivastigmine patch for three months. However, five patients reported skin eruptions or erythema and itching at the site of application during the run-in period of four weeks. They were excluded from this study because of skin problems attributed to rivastigmine transdermal patch. Finally, fourteen patients achieved a target patch size of 10 cm² rivastigmine patch from the initial patch application (Fig. 1). After 12 weeks from baseline sleep and neurocognitive studies, a follow up sleep and neurocognitive study was performed in these fourteen patients. They were 68.4±4.3 [mean±standard deviation(SD)] years old, and included five males and nine females. Their body mass index was 23.8±2.9 (mean±SD) kg/m².

Table 1. Polysomnographic and cognitive outcome measures

| Parameter                  | Baseline     | After treatment | Interaction p |
|---------------------------|--------------|-----------------|---------------|
| Total sleep time (mins)   | 283.3±62.7   | 249.9±85.7      | 0.288         |
| Stage 1 sleep (%)         | 21.9±14.6    | 18.6±13.1       | 0.394         |
| Stage 2 sleep (%)         | 53.3±18.7    | 55.9±13.1       | 0.863         |
| Stage 3 sleep (%)         | 17.0±2.5     | 12.0±14.1       | 0.571         |
| REM sleep (%)             | 14.9±9.5     | 22.3±25.2       | 0.367         |
| Total wake time (mins)    | 142.0±56.2   | 168.9±77.1      | 0.481         |
| WASO (mins)               | 113.8±60.2   | 172.5±114.6     | 0.170         |
| Latency to sleep onset (mins) | 28.2±26.8 | 37.5±39.8       | 0.942         |
| Sleep efficiency (%)      | 66.4±13.3    | 59.0±20.1       | 0.347         |
| Respiratory Disturbance Index (/hr) | 45.3±18.4 | 28.4±14.4       | 0.023         |
| Apnea Hypopnea Index (/hr) | 41.1±12.4   | 24.7±18.2       | 0.018         |
| PLMS Index (/hr)          | 34.0±36.0    | 29.9±36.4       | 0.053         |
| Epworth Sleepiness Scale  | 7.3±4.8      | 9.3±4.0         | 0.491         |
| Stanford Sleepiness Scale | 2.5±1.9      | 2.5±1.7         | 0.849         |
| ADAS-cog score            | 31±10.1      | 22.5±5.9        | 0.199         |

ADAS-cog: Alzheimer’s disease assessment scale-cognitive, PLMS: periodic limb movement during sleep, REM: rapid eye movement, WASO: wake time after sleep onset.

Effect of rivastigmine transdermal patches on sleep and cognitive function

TST, TWT and proportion of N1, N2, N3 and REM sleep showed no statistical difference between the baseline and follow up values after rivastigmine patch application. The WASO, SL, SE, and PLMS index also did not show any difference from treated 5 cm² rivastigmine patch per day for 4 weeks. In the absence of any adverse events related with the patch, patients were treated to 10 cm² rivastigmine patch for three months. However, five patients reported skin eruptions or erythema and itching at the site of application during the run-in period of four weeks. They were excluded from this study because of skin problems attributed to rivastigmine transdermal patch. Finally, fourteen patients achieved a target patch size of 10 cm² rivastigmine patch from the initial patch application (Fig. 1). After 12 weeks from baseline sleep and neurocognitive studies, a follow up sleep and neurocognitive study was performed in these fourteen patients. They were 68.4±4.3 [mean±standard deviation(SD)] years old, and included five males and nine females. Their body mass index was 23.8±2.9 (mean±SD) kg/m². Education status of enrolled patients was 4.02±3.04 (mean±SD) years, and K-MMSE was 19±3.0 (mean±SD) at the baseline level. ADAS-cog was 31±10.1 (mean±SD) at baseline level. All these patients did not consume coffee or caffeine containing tea. Three patients (two males, one female) reported initiation insomnia as well as SDB. One of these patients was on antihypertensive drug for 10 years. The other patients had no vascular risk factors such as diabetes, hyperlipidemia and hypertension, stroke or cardiac problems.
the baseline levels after treatment. However, RDI and AHI (28.4±14.4 and 24.76±28.2, respectively) markedly decreased after the rivastigmine patch treatment (p<0.05) compared to RDI and AHI at baseline level (45.3±18.4 and 41±12.4, respectively). ESS and SSS from the sleep questionnaire showed no differences between baseline and after treatment. The sleep study findings are summarized in Table 1. The K-MMSE and CDR were 19±3.0 and 1.2±0.4 (mean±SD) at the baseline level, and 18±3.0 and 1.3±0.66 (mean±SD) after rivastigmine patch application, respectively; ADAS-cog scores were 31±10.1 (mean±SD) at baseline and 22.5±5.9 (mean±SD) after treatment. However, there was no statistical significance of cognition and in the functional state before and after rivastigmine transdermal patch treatment. These results are outlined in Table 1.

**DISCUSSION**

Several studies support the association between sleep apnea and AD. SDB reported a high prevalence (33% to 60%) of patients with AD, and is considered as an important non-cognitive symptom contributing to three clinical courses of AD. SDB is often reported to have an association with agitation or day time somnolence, other than cardiovascular risk, in patients with AD. Therefore, treatment of SDB is considered to be a significant issue in the management of patients with AD. Ancoli-Israel et al. reported that continuous positive airway pressure (CPAP) reduced daytime somnolence in patients with mild to moderate AD with SDB. Cooke et al. reported that the long-term CPAP treatment for patients with AD and SDB may result in improvements of sleep and mood, as well as a slowing cognitive deterioration. Especially for patients with dementia, it is difficult to maintain CPAP therapy because most of the cognitive behavioral problems are aggrated during night time sleep. In contrast to previous studies on physical and surgical treatment for SDB, there is a dearth of effective pharmacological approaches. Very few studies have examined the effects of cholinergic treatment on sleep in patients with AD. A study on the effects of tacrine on REM sleep was not conclusive, probably since doses higher than 100 mg per day could not be administered due to hepatotoxicity. PSG data by Moraes et al. reported that donepezil inhibits acetylcholinesterase improved obstructive sleep apnea and increased REM sleep density and periods in patients with AD. No evidence of worsening sleep or nightmares were found in the above study. Suckys-Claudino et al. showed that donepezil treatment improved RDI, oxygen desaturation, and sleepiness. These studies with donepezil support the conceptual opinion that cholinergic transmission might influence breathing regulation in patients with AD/SDB. Meanwhile, rivastigmine transdermal patches are another form of acetylcholinesterase and butryrylcholinesterase inhibitors, which are currently approved for the treatment of patients with probable AD. A transdermal form of rivastigmine has several advantages, including continuous delivery with reduced fluctuation of plasma drug levels, improved tolerability, easy administration of optimal doses, and preference for caregivers. We expect and focus the stable cholinergic properties of rivastigmine patches to be tolerated by our enrolled subjects; however, adverse events, such as skin rash or itching sensation, developed in a few patients after rivastigmine patch application. The present study demonstrated that rivastigmine patch treatment has the potential to reduce RDI and improve sleep apnea or hypopnea, but did not changed other sleep parameters, namely sleep latency, SE, WASO or REM sleep density and periods. Another finding is that improved RDI of patients with AD on rivastigmine patch treatment was not statistically significant when correlated to cognitive function measured by ADAS-cog. To the best of our knowledge, this is the first PSG study on the effect of rivastigmine transdermal patches in patients with probable AD. Until now, most cholinergic drugs mainly increase the REM density and decrease the latency of REM onset. However, several studies have shown contradictory results, depending on the subjects or drugs enrolled in each study. In particular, a recent study of rivastigmine in elderly persons significantly reduced the REM latency, while there was no effect on REM sleep proportion. In our study, the rivastigmine patch treatment did not affect the proportion of REM sleep or latency to REM onset, and REM density. We suggest that a large sample longitudinal study would be appropriate to estimate the effect of rivastigmine during REM sleep. In degenerative conditions such as dementia, the decreased thalamo-pontine cholinergic projections may affect the respiratory drive, leading to both central and obstructive sleep apnea. Based on this mechanism, increasing the cholinergic tone by ChEIs in thalamopontine cholinergic projections could improve SDB. We consider that the cholinergic action of rivastigmine transdermal patch is the main mechanism for improving SDB. In contrast, enhancing REM sleep of ChEIs might affect sleep apnea in a negative way, in spite of its positive effect to impaired cognitive functions. Such conflicting effects make it difficult to understand the actual mechanisms. A possible explanation is that rivastigmine increases the central cholinergic transmission in areas related to different tasks, including cognitive function, REM sleep generation and regulation. We suggest that further studies for the cholinergic effects of ChEIs on REM sleep and SDB should be conducted to confirm our conclusion. In our
Conflicts of Interest

The authors have no financial conflicts of interest.

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