Psychiatry Research 251 (2017) 312–318

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Effects of donepezil on sleep disturbances in patients with dementia with Lewy bodies: An open-label study with actigraphy☆

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ARTICLE INFO

Keywords:
Cholinesterase inhibitor
Treatment
Neuropsychiatric inventory
Fragmented sleep
Body activity
Cognitive impairment
Delusions

ABSTRACT

We investigated whether donepezil, a cholinesterase inhibitor, can be used to treat sleep disturbances in patients with dementia with Lewy bodies (DLB). Sleep disturbances were evaluated with the sleep disturbances item of the Neuropsychiatric inventory (NPI) and an actigraph in 16 DLB patients and 24 normal elderly control (NC) subjects. The presence/absence of nine kinds of sleep symptoms, such as dream enactment, were also evaluated in the DLB patients. The DLB patients were then given 5 mg/day donepezil for 14 weeks and evaluated again. Eight of the 16 DLB patients had some sleep disturbances before taking donepezil. The actigraphy data indicated that average activity count per minute in sleep (AAC), which reflects body activity at night, was significantly higher and total sleep time was significantly longer in DLB patients than in NC subjects. The NPI sleep disturbances score significantly improved and the number of DLB patients who had sleep disturbances decreased after taking donepezil. The actigraphy results indicate that the sum of all wake epochs within the sleep period, which reflects the degree of fragmented sleep, and the AAC decreased in the DLB patients after donepezil treatment. These results indicate that donepezil treatment reduced sleep disturbances in DLB patients.

1. Introduction

Sleep disturbances, such as early awakening, increased nocturnal awakenings, and sundowning, are highly prevalent in patients with dementia (Mayer et al., 2011). Dementia with Lewy bodies (DLB) patients constitute the second largest group of patients with dementia after Alzheimer's disease (AD) (McKeith et al., 2004). Sleep and nighttime behavior disorders are more frequently associated with DLB than they are with AD (Boddy et al., 2007; Chwiszczuk et al., 2016; Grace et al., 2000; Hashimoto et al., 2015; Rongve et al., 2010). Rapid eye movement (REM) sleep behavior disorder (RBD) is a well-known symptom of DLB and is one of the suggestive features in the consensus clinical diagnostic criteria for DLB (McKeith et al., 2005). DLB patients also show frequent nocturnal awakening, sleep talking, bad dreams, excessive daytime somnolence, confusional arousals, and sleep apnea (Pao et al., 2013; Terzaghi et al., 2013). Moreover, they show disturbances of movement control during sleep, such as periodic limb movements.

Cholinergic neurotransmission was found to be more defective in DLB than in AD (Perry et al., 1994). In DLB, cholinergic losses affect presynaptic nuclei in both the brainstem and basal forebrain, while postsynaptic cortical muscarinic and nicotinic receptors are more functionally intact (Perry et al., 1993), suggesting that cholinesterase inhibitors (ChEIs) may be effective in treating DLB. In fact, ChEIs have

Abbreviations: DLB, Dementia with Lewy bodies; AD, Alzheimer's disease; REM, Rapid eye movement; RBD, REM sleep behavior disorder; ChEI, Cholinesterase inhibitor; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; MRI, Magnetic Resonance Images; NC, Normal elderly control; WMS-R, Wechsler Memory Scale-Revised; A/C, Attention/concentration; LF, Letter Fluency test; VPTA, Visual Perception Test for Agnosia; NPI, Neuropsychiatric inventory; MFQ, Mayo fluctuation questionnaire; TB, Time in Bed; SL, Sleep Latency; SP, Sleep Period; SnT, Snooze Time; WASO, Wake after sleep onset; TST, Total sleep time; SE, Sleep efficiency; AAC, average activity count per minute in sleep; PSG, Polysomnography

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http://dx.doi.org/10.1016/j.psychres.2017.02.039
Received 16 June 2016; Received in revised form 2 February 2017; Accepted 18 February 2017
Available online 20 February 2017
0165-1781/

positive global effects (Wang et al., 2015) and are effective at treating neuropsychiatric symptoms in patients with DLB (Cummings et al., 2016; Stinton et al., 2015). A recent systematic review did not find any evidence that one ChEI, donepezil, was effective at treating sleep disturbances in AD patients (Cummings et al., 2016). However, another ChEI, rivastigmine, was reported to improve several disorders (frequent nocturnal awakening, sleep talking, bad dreams, nocturnal agitation, and daytime somnolence) in six of seven DLB patients (Maclean et al., 2001). Rivastigmine was also effective at treating bad dreams, confusion on waking, and periodic limb movements in two of six DLB patients (Grace et al., 2000). In these studies, sleep disturbance in DLB patients was evaluated with observational or subjective scales, such as the neuropsychiatric inventory (Grace et al., 2000; Maclean et al., 2001) and with questionnaires on sleep disturbance, the Stavanger Sleep Questionnaire and the Epworth Sleepiness Scale (Grace et al., 2000), rather than by objective methods.

Only one case report examined the effect of donepezil on sleep disturbance in a DLB patient (Ozaki et al., 2012). In that study, donepezil was found to diminish night screaming and increase sleep spindle as measured by polysomnography (PSG), the gold standard method for evaluating sleep disturbance. Although PSG has been used to measure sleep disturbance in patients with AD (Mizuno et al., 2004) and DLB (Ozaki et al., 2012; Pao et al., 2013; Terzaghi et al., 2013), its use requires extensive cooperation with the patients. Thus, PSG does not always work well for DLB patients who have cognitive impairment, fluctuating cognition, and intense movement which they cannot control during sleep.

The wrist actigraph is a watch-like device that detects wrist movements and uses the data to calculate a number of sleep parameters. Some actigraphs also measure light intensity, which can be used to estimate when the patient was in bed. Actigraphy, after recent improvements in hardware and software, is reported to be sufficiently sensitive to detect the effects of interventions targeting insomnia (Kwok et al., 2013). The use of actigraphy in patients with dementia has increased in the past decade (Camargos et al., 2013; Mulin et al., 2011). The advantages of actigraphy include the feasibility of home-based assessments for individuals who do not tolerate sleeping in an unfamiliar environment, such as in the laboratory, and the capability of providing objective measurements that are representative of daily variations and sleep quality and a tendency to not be influenced by patient expectations or recall bias.

Here, we conducted an open-label study to evaluate the effects of donepezil on sleep disturbances at night in 16 patients with DLB, in which sleep disturbances were objectively evaluated with actigraphy. We also evaluated the association between improvement of sleep disturbances and improvement of other neuropsychiatric and cognitive impairment after donepezil treatment in the DLB patients.

2. Methods

2.1 Subjects

2.1.1 DLB patients

Patients who met the consensus diagnostic criteria (McKeith et al., 1996) for probable DLB were recruited from the neuropsychological clinic of the Department of Neuropsychiatry of Osaka University Medical Hospital from October 2008 to May 2014. The subjects were outpatients 60–85 years old) with mild to moderate dementia (10–26 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Clinical Dementia Rating (CDR) (Gelb and St Laurent, 1993)≧0.5). Causes for exclusion from this study included diabetes mellitus, abnormal findings on Magnetic Resonance Images (MRI) other than brain atrophy, complication or history of dementia other than DLB, psychiatric disease, physical disorders that affect brain function, severe complication of cardiovascular, hepatic, renal, or other diseases, severe digestive ulcers, severe asthma or obstructive lung disease, lack of a caregiver who knew patient well and could keep a sleep diary of the patient, and treatment with ChEIs or any drugs approved for investigation but not for general use.

2.1.2 Normal elderly control (NC) subjects

We recruited 24 cognitively normal elderly volunteers (10 males and 14 females) as controls from October 2008 to May 2011. Inclusion criteria were (1) 70–85 years old, (2) subjectively and objectively normal cognition (MMSE≧24 and CDR=0), (3) no history of neurological or psychiatric disease or physical disorder that affects brain function, and (4) no abnormal findings on MRI.

Written informed consent was obtained from the patients when possible, from their caregivers and from the NC subjects before initiating the study procedures. The study was conducted in compliance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki (2002) of the World Medical Association and approved by the Research Ethical Committee of Osaka University Hospital (Suita, Japan). This study was registered with ClinicalTrials.gov, number NCT00776347.

2.2 Procedures

2.2.1 Design

The present study was designed as an open-label treatment study of patients with mild to moderate DLB. Patients who had consented to participation in the study and who fulfilled the inclusion criteria were registered. They underwent baseline assessment of clinical features and sleep disturbances. Then, they received 3 mg/day donepezil after breakfast for 2 weeks and then 5 mg/day donepezil for the next 14 weeks. We assumed that the severity of dementia as rated by the CDR were 0.5, 1 or 2 in DLB patients who were recruited in this study. Therefore, the dosage of donepezil for DLB patients in this study was determined according to the regular dosage of donepezil for patients with AD in Japan: 5 mg/day donepezil for AD patients with CDR 0.5, 1 and 2. Adverse events and medication compliance of the patients were checked at weeks 2, 6, 10, 14, and 16. The DLB patients were assessed again between 14 and 16 weeks after the administration of donepezil. The use of ChEIs other than donepezil, antipsychotic agents, antiparkinson drugs (other than L-dopa or dopamine agonists), yokukansan and yokukansan-ka-tinpihange were not allowed during the study. If any patients were required to continue taking drugs, such as benzodiazepines, sleep medication, antidepressants, L-dopa, dopamine agonists, or cerebral ameliorators during the study, they were prohibited from changing the dose of the drugs during the study. Clinical features and sleep disturbances of the NC subjects were assessed once.

2.2.2 Assessments of clinical features

Cognition was assessed using the MMSE (Folstein et al., 1975). In addition, 3 cognitive domains (attentive, executive, and visuoperceptual functions) relevant to DLB were assessed using the Wechsler Memory Scale-Revised (WMS-R) attention/concentration (A/C) subscale (Wechsler, 1987), the Letter Fluency test (LF) (Ito et al., 2004), and the Visual Perception Test for Agnosia (VPTA) form discrimination and overlapping figure identification subscales (Japan Society for Higher Brain Dysfunction, 2003). A higher score indicates better performance on the MMSE, WMS-R, and LF but worse performance on the VPTA.

Behavior was assessed using the Neuropsychiatric inventory (NPI)-plus (Mori et al., 2012), which included the original NPI-10 (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior) (Cummings et al., 1994) plus 2 additional symptoms associated with DLB: sleep disturbances (Cummings, 1997) and cognitive fluctuation (Mori et al., 2006). Cognitive fluctuation was also assessed with Mayo fluctuation questionnaire (MFQ) (Escandon et al., 2010). Caregivers of DLB patients and family members who lived with NC subjects