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CASE REPORT

Improvement in Sundowning in Dementia with Lewy Bodies after Treatment with Donepezil

ARVID SKJERVE[1]* AND HARALD A. NYGAARD[2]
[1]*Olaviken Behandlingssenter, Bergen, Norway*
[2]*Department of Public Health and Primary Health Care, Section for Geriatric Medicine, University of Bergen, Norway*

ABSTRACT

Sundowning, manifested as a recurring increase in restlessness and agitation in the evening, is described in a 71-year-old man with clinically diagnosed dementia with Lewy bodies. An objective measure of activity using the activity electronic monitoring technique indicated a marked increase in activity level during the evening compared to earlier in the day. After treatment with donepezil, a cholinesterase inhibitor, ratings of behavioural symptoms improved. In addition, there was a marked reduction in evening activity and an increase in daytime activity. Cognition and parkinsonism also improved. Possible explanations for this finding are discussed. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS—sundowning; dementia with Lewy bodies; donepezil; activity rhythm

INTRODUCTION

Sundowning refers to the recurring onset of confusion or agitation in elderly patients in the evening and can be a significant clinical problem (Evans, 1987; Bliwise, 1994; Little *et al*., 1995). In community dwelling patients with Alzheimer's disease (AD), the phenomenon has been reported to be associated with significant caregiver stress (Gallagher-Thompson *et al*., 1992), and probably contributes to an increased risk of premature institutionalisation. Sundowning is reported to occur in a quarter to a third of AD patients (Devanand *et al*., 1992; Little *et al*., 1995).

Sundowning shares similarities with delirium, e.g. attention deficits and activity disturbances. However, contrary to delirium, sundowning seems to persist for a longer period of time, and is not associated with acute medical illness, nor with increased mortality as in delirium (Little *et al*., 1995). Furthermore, due to its predictable occurrence at specific times of the day, a disturbance of the 24-hour circadian rhythm is assumed. Studies of rest–activity rhythm using electronic activity monitors have shown a delay in peak daily activity in AD patients (Satlin *et al*., 1991; Ghali *et al*., 1995; Ancoli-Israel *et al*., 1997). Increased activity late in the day corresponds with clinical studies revealing that restlessness is a common behaviour in sundowning (Evans, 1987; Little *et al*., 1995). The suprachiasmatic nucleus (SCN) is probably involved in generating and regulating the circadian rhythm, and neuropathological changes in SCN in AD are assumed to be involved in the observed rhythm disturbances (Swaab *et al*., 1985; Stopa *et al*., 1999). In addition, the inadequate influence of external 'Zeitgebers' such as social conventions and daylight may also contribute to the disturbances (Campbell *et al*., 1988; Ancoli-Israel *et al*., 1997).

Various intervention strategies have been suggested to overcome sundowning, but few studies have been performed using sundowning as an outcome measure (McGaffigan and Bliwise, 1997). In the present case report, we observed improvement in sundowning in a patient with dementia with Lewy bodies (DLB) after treatment with donepezil, a cholinesterase inhibitor. Donepezil has previously been reported to improve cognition,

* Correspondence to: A. Skjerve, Olaviken Behandlingssenter, 5306 Erdal, Norway. Tel: +47-55349650. Fax: +47-55349651. E-mail: arvid.skjerve@hordaland-f.kommune.no

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ADL functioning and hallucination in DLB cases (Shea *et al*., 1998; Aarsland *et al*., 1999).

CASE STUDY

A 71-year-old man with probable DLB according to consensus criteria (McKeith *et al*., 1996) was referred from a general nursing home to a psychogeriatric inpatient unit in June 1998 because of severely agitated behaviour. His cognitive and functional impairment had gradually progressed over 3 years, and was accompanied by visual hallucinations and delusions, parkinsonism, fluctuating consciousness and repeated falls. Symptoms of parkinsonism with bradykinesia and rigidity and cognitive symptoms concurrently occurred. A cerebral CT scan showed general cortical atrophy.

According to primary caregivers and medical notes, his agitated and restless behaviour increased in the evening and at night, a pattern that had persisted for more than 2 years. The severity of the behaviour symptoms by and large remained unchanged by therapeutic trials with melperon, oxazepam, citalopram or haloperidol, as well as during drug-free periods, and his parkinsonism exaggerated markedly while being treated with haloperidol. No precipitating medical condition or drug could be attributed as the cause for his confused state.

At admittance neuropsychological testing indicated moderate cognitive deficits most pronounced for visuoconstructive and executive functions. The Mini Mental Status Examination (MMSE; Folstein *et al*., 1975) score was 11/30 points. During the first 4 months at the psychogeriatric ward, treatment with risperidone, oxazepam and citalopram alone or in combination had no striking effect on his condition, although some reduction in delusions and visual hallucinations was observed after treatment with risperidone (1 mg/day). He developed peripheral edemas, but repeated physical examinations, including chest X-ray, did not reveal any medical condition, which could explain these symptoms. In particular, no congestive heart failure was detected. There was no improvement in his parkinsonism during these months, as evaluated by a geriatrician and the nursing staff, nor in his behaviour. Rating of behavioural and psychological symptoms using the Cohen-Mansfield Agitation Inventory (CMAI; Cohen-Mansfield *et al*., 1989) and the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD; Reisberg *et al*., 1987) indicated a high level of wandering, pacing and general restlessness, but also aggressiveness, hallucinations and anxieties. Nurses trained in using CMAI and BEHAVE-AD performed the ratings. The staff reported that these symptoms were more frequent during the evening compared to earlier in the day.

The increased wandering and restlessness in the evening was indirectly confirmed by objective measures of activity using the electronic activity monitoring technique (Actiwatch Monitoring System, Cambridge Neurotechnology Ltd). The Actiwatch was placed on the patient's non-dominant arm for 24 hours a day for five subsequent days (Tuesday to Saturday; 120 hours). An accelerometer in the Actiwatch monitors the occurrence and degree of motion. Activity data were collected during 1-minute epochs. For analysis of the activity pattern, calculations included percentage of daytime activity level (from 8 a.m. to 4 p.m.) and evening activity level (from 4 p.m. to 12 p.m.) to averaged 24-hour activity. An activity level of $>100\%$ for a given period indicates a higher activity level during this period compared to the mean activity level for the whole period. For the 5 days, the mean evening activity level was 175% and daytime activity level was 82%, which means that activity level was considerably higher during the evening. Furthermore, calculation of the mean time of peak daily activity (cosinor analysis performed by the Actiwatch system software), showed that the time of the peak was at 7.45 p.m. (range 6.45–8.15 p.m.).

Treatment

In October 1998 donepezil (5 mg/day) was prescribed, 7 days after discontinuation of all psychotropic drugs (risperidone 1 mg/day, oxazepam 10 mg/day and citalopram 10 mg/day). During the drug-free period, there was no change in the level of agitation, although some improvement in parkinsonism was observed. No major changes in non-psychotropic drugs were done before or after treatment onset.

A marked improvement in the patient's behaviour was observed 10 days after the prescription of donepezil. The condition improved further during the following weeks, which was also reflected by changes in MMSE, CMAI and BEHAVE-AD scores, rated 6 and 14 weeks after the initiation of treatment (Table 1). Virtually no behaviour disturbance was recorded on the CMAI and BEHAVE-AD scales.

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Table 1. Ratings on MMSE, CMAI and BEHAVE-AD, and time of peak daily activity before and after treatment with donepezil (score range)

	Weeks before		Weeks after	
	5	1	6	14
MMSE (0–30*)	11	11	20	21
CMAI (29*–203)	51	55	34	34
BEHAVE-AD (0*–75)	12	19	0	0
Peak daily activity p.m.	7.45	–	5.00	–

MMSE, Mini-Mental State Examination; CMAI, Cohen-Mansfield Agitation Inventory; BEHAVE-AD, The Behavioural Pathology in Alzheimer's Disease Rating Scale.
* Perfect score.

Recordings of activity which were performed over 5 days (Tuesday to Saturday) 6 weeks after initiation of treatment, showed a marked decrease in evening activity level from 175 to 138%, and an increase in daytime activity level from 82 to 125% compared to the previously mentioned activity levels that were measured 5 weeks before treatment (Fig. 1). There was also an advance in the mean time of peak daily activity of about 3 hours from before to after treatment (after 5.00 p.m., range 3.30–5.30 p.m.; Table 1).

Furthermore, his edemas almost vanished, and there was an apparent improvement in motor rigidity and bradykinesia. Donepezil (5 mg) was well tolerated. His behaviour remained stable, and he was subsequently discharged to a general nursing home.

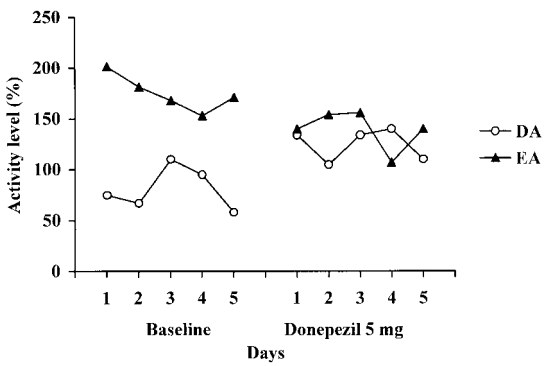

Figure 1. Percentage of daytime (DA; 8 a.m.–4 p.m.) and evening (EA; 4 p.m.–12 p.m.) activity level to daily 24-hour activity level in 5-day periods, 5 weeks before and 6 weeks after treatment with donepezil

DISCUSSION

Previous reports have described the efficacy of donepezil in cognitive function and psychiatric symptoms in patients with DLB (Shea *et al*., 1998; Aarsland *et al*., 1999). In addition to an improvement in these symptoms, the present case also describes a marked improvement in sundowning indicated by a reduction in agitated behaviour, rated by well-known scales, and a reduction in objective measures of evening activity.

The core features of DLB with fluctuations, visual hallucinations and motor parkinsonism, and also supportive features including deficits in visuospatial and executive functions, repeated falls and neuroleptic sensitivity, were present (McKeith *et al*., 1996). Although a diagnosis of AD cannot be excluded, the symptom pattern is not typical for AD. Parkinson's disease is also less likely, because the parkinsonian symptoms were relatively mild, and cognitive deficits occurred simultaneously. Furthermore, drug induced parkinsonism was less likely because the symptoms were also observed during drug-free periods.

Sundowning in DLB may have similar causes to sundowning in AD. The hypothesis of disturbed circadian rhythm in sundowning implies that the regulation of the rhythm is disturbed by neuropathological changes in steering brain regions, such as the SCN (Swaab *et al*., 1985; Stopa *et al*., 1999). In addition, an inadequate influence of external time cues (daylight, social factors) may also contribute to disturbances in the rhythm. The improvement in sundowning may be secondary to improved cognitive functioning with donepezil. The patient obviously became more capable of perceiving and interpreting his surroundings, including social time cues, which may have resulted in an improvement in stabilisation of the circadian rhythm. Animal and tissue studies support the role of cholinergic influences on the rhythm (Liu and Gillette, 1996; O'Hara *et al*., 1998). Reduced cholinergic activity in DLB may, therefore, induce circadian rhythm disturbances including sundowning, which are counteracted by cholinergic reinforcement.

There are some alternative explanations for the observed improvements in this patient. With a washout period of 7 days prior to donepezil treatment, it may be argued that a discontinuation of psychotropic drugs was responsible for the observed improvements. The marked improvement of MMSE may indicate that these drugs had a sedative effect. Sundowning also has similarities

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with delirium, and it is possible that donepezil beneficially influenced a delirious state (Wengel *et al*., 1998). In our opinion, the symptoms of this patient fit in well with the symptoms of sundowning rather than delirium.

We also observed a reduction in edemas in the patient's extremities after treatment. We assume that this was related to the increased activity during the daytime. In addition, there was an improvement in bradykinesia, also reported in another DLB case (Aarsland *et al*., 1999). Risperidone may induce extrapyramidal symptoms in dementia (Geroldi *et al*., 1997), and discontinuation of the drug might have improved these symptoms. However, parkinsonism was present before initiation of risperidone.

In summary, this study reports an improvement in sundowning in DLB after treatment with donepezil, and an improvement in the clinical observations of agitation and behaviour was supported by changes in objective measures of activity. The limitation of a single-case study makes further studies necessary in order to see whether donepezil or other cholinesterase inhibitors induce similar improvements in sundowning in other DLB cases or samples.

Note. The patient and his wife have given consent for the information contained in this report and the intervention outlined to be published.

KEY POINTS

- Sundowning in dementia is assumed to be related to circadian rhythm disturbances.
- In a case of DLB, improvement in sundowning was observed after treatment with donepezil.
- One possible explanation might be that cholinergic drugs improve processes involved in circadian regulation.

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