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ORIGINAL ARTICLE

Efficacy of a high dosage of donepezil for Alzheimer's disease as examined by single-photon emission computed tomography imaging

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Abstract

Background: The efficacy of donepezil 10 mg/day against Alzheimer's disease (AD) was examined, with a primary focus on changes in cerebral blood flow (CBF) as determined by single-photon emission computed tomography imaging.

Methods: The subjects were 24 outpatients who had been diagnosed with probable AD, which had progressed to advanced AD. Mini-Mental State Examination and Alzheimer's Disease Assessment Scale (ADAS) scores were determined before and after the donepezil dosage increase. ^{99m}Tc-ethylcysteinate dimer single-photon emission computed tomography was performed to evaluate changes in CBF. Then, a comparative study evaluated changes after the donepezil dosage increased.

Results: After the donepezil dosage increase, adverse effects associated with gastrointestinal symptoms were observed in one patient, and irritability was observed in three. The average Mini-Mental State Examination score changed from15.25 ± 6.24 to 14.67 ± 6.07; significant changes were not observed. Seventeen subjects were evaluated with the Alzheimer's Disease Assessment Scale-cognitive subscale. After the dosage increase, the average subscale score decreased from 24.52 ± 13.39 to 21.56 ± 9.14, and significant improvement was observed ($P = 0.021$). With respect to changes in the CBF, the values of all three indicators decreased after the higher dosage increased CBF. However, no significant differences were observed in CBF. Analysis performed after the donepezil dosage increase revealed significant increases in CBF in the right occipital and temporal lobes, left temporal lobe, right parietal lobe, and both parts of the posterior cerebellum.

Conclusion: Increasing the donepezil dosage from 5 mg/day to 10 mg/day is effective for the treatment of AD.

INTRODUCTION

In Japan, up to 10-mg/day donepezil hydrochloride was approved to treat severe Alzheimer's disease (AD) in August 2007. Until recently, the ameliorative effects of donepezil hydrochloride on cognitive function had only been reported in cases of mild to moderate AD.[1,2] (In Japan, the normal dosage for mild to moderate AD is 5 mg/day.) However, it was recently reported that donepezil hydrochloride is effective against advanced AD as well.[3–5]

Approval of larger dosages has raised concerns over the increased incidence of adverse effects, including gastrointestinal symptoms and increased restlessness, associated with the dosage of 10 mg/day. Moreover, there has been difficulty in determining the timing and indications for an increase in dosage. Therefore, by focusing primarily on changes in cerebral blood flow (CBF), this study prospectively examined the therapeutic effects of increasing severe AD patients' dosage to

10 mg/day after they had been on long-term doses of 5 mg/day.

METHODS

Subjects

The subjects of this study were 24 outpatients (6 men, 18 women; average age: 77.6 years) who were diagnosed with probable AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association diagnostic criteria. The patients had shown progression of symptoms and severe dementia after receiving a donepezil hydrochloride dosage of 5 mg/day for at least 4 months. At the initial examination, subjects' average Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores were 18.72 ± 6.54 and 18.43 ± 8.71, respectively. The average duration of donepezil hydrochloride administration was 1111 ± 919 days, and the MMSE and ADAS scores estimated immediately before the dosage was increased to 10 mg/day were 15.25 ± 6.24 and 24.52 ± 13.39, respectively. The average duration of donepezil hydrochloride administration until the time of evaluation was 211 ± 107 days.

Evaluation of apolipoprotein E (ApoE) phenotype expression in 19 subjects, in whom this expression could be evaluated, revealed expression of the ApoE 4/4, ApoE 3/3, and ApoE 4/3 phenotypes in 1, 7, and 11 cases, respectively. Patient background details are shown in Table 1.

Methods

To evaluate the efficacy and safety of the increased dosage, the donepezil hydrochloride dosage in the 24 subjects was increased from 5 mg/day to 10 mg/day. The efficacy of the increased dosage was evaluated by conducting tests to determine the MMSE and ADAS-cog scores 6 months before and 1 year after increasing the dosage and by comparing the results. Statistical processing was performed by testing the data with the Student's *t*-test using GraphPad Prism statistics software (San Diego, CA, USA).

Similarly, imaging evaluation was conducted by performing ^{99m}Tc-ethylcysteinate dimer single-photon emission computed tomography (SPECT) on two occasions: within 1 month before and 6 months after increasing the dosage of donepezil hydrochloride to 10 mg/day. Changes in CBF were evaluated according to the disease-specific region analysis method of Matsuda *et al*., which examines decrease in a specific region's blood flow (severity), the proportion of the specific region showing the decrease in blood flow (extent), and the ratio of the decrease in blood flow in the brain to that in the specific region (ratio).[6] These factors were measured with the easy Z-score imaging system (eZIS) and the findings were compared. Changes in CBF after the donepezil hydrochloride dosage was increased were compared using Statistical Parametric Mapping 8 (SPM8, Professor Karl Friston, University College London, London, UK), which runs on MATLAB (MathWorks, Sherborn, MA, USA). Twenty-three outpatients at Hachioji Medical Center (Tokyo, Japan) volunteered to participate as part of the normal control group; the volunteers did not have dementia but were undergoing treatment for other conditions

The expression of the ApoE phenotype in these subjects was evaluated to determine whether the efficacy of the increased donepezil hydrochloride dosage varies according to the phenotype's expression.

Table 1 Patient backgrounds

Disease	Alzheimer's disease in all cases
Sex (men : women)	6:18
Age (years) (mean ± SD)	77.6 ± 5.2
Initial MMSE, and ADAS-cog score (mean ± SD)	MMSE: 15.25 ± 6.24 ADAS: 24.52 ± 13.39
MMSE, and ADAS-cog score at donepezil increasing 10 mg/day (mean ± SD)	MMSE: 14.67 ± 6.07 ADAS: 21.56 ± 9.14
Duration of 5 mg/day of donepezil (mean ± SD)	1111 ± 919 days
Duration of 10 mg/day of donepezil (mean ± SD)	211 ± 107 days
ApoE phenotype	3/3: 7 cases, 4/3:11 cases, 4/4:1 case

ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive; ApoE, apolipoprotein E; MMSE, Mini-Mental State Examination.

Ethical considerations

Informed written consent was obtained from all subjects and their families for blood collection, brain imaging, and psychological testing.

RESULTS

After the increase in the donepezil hydrochloride dosage to 10 mg/day, adverse effects associated with gastrointestinal symptoms (nausea) were observed in one subject and irritability was observed in three subjects. Therefore, administration of the increased dosage was discontinued in these four subjects

(16.7%). The remaining 20 subjects showed favourable tolerability to the increased dosage and continued to receive it.

After the dosage increase, the average MMSE score changed from 15.25 ± 6.24 to 14.67 ± 6.07; the difference in the score was not significant. ADAS-cog evaluation was conducted for 17 subjects; three subjects who did not cooperate were excluded. The average MMSE score of these 17 cases changed from 15.58 ± 5.2 to 14.82 ± 4.91; the difference in the score was not significant. The average MMSE score of the three excluded cases was 5.67 ± 0.33, which was significantly lower than the average MMSE score of the 17 cases that underwent ADAS.

The average ADAS scores decreased from 24.52 ± 13.39 to 21.56 ± 9.14 after the donepezil hydrochloride dosage increase, and significant improvements were observed ($P = 0.021$) (Figs 1,2).

No significant correlations were found in the relationship between ameliorative the effects on cognitive function attributable to the increased dosage of donepezil and the affected period of Alzheimer's dementia, the duration of administration of donepezil at 5 mg/day, or the degree of cognitive function impairment.

SPECT was used to determine changes in CBF before and after the dosage increase to 10 mg/day. Based on the three indicators defined by Matsuda *et al*.,[6] values from SPECT were compared in eZIS, which revealed the following findings: severity changed from 2.23 ± 1.26 to 2.13 ± 0.98, extent changed from 40.76 ± 25.49% to 38.55 ± 25.39%, and ratio changed from 2.94 ± 1.83 times to 2.79 ± 1.98 times. Thus, values of all three indicators decreased after the donepezil hydrochloride dosage increased. The findings did not suggest a tendency toward increased CBF in a specific region after the dosage was increased, and no significant differences were observed (Table 2, Figs 3–5).

SPM8 analysis revealed significant increases in blood flow in the right occipital lobe, right temporal lobe, a portion of the left temporal lobe, right parietal lobe, and both parts of the posterior cerebellum after the dosage was increased to 10 mg/day. Furthermore, significant decreases in CBF were observed in the left frontal lobe, an extremely small portion of the right frontal lobe, and a portion of the right parietal lobe ($P < 0.05$) (Figs 6,7).

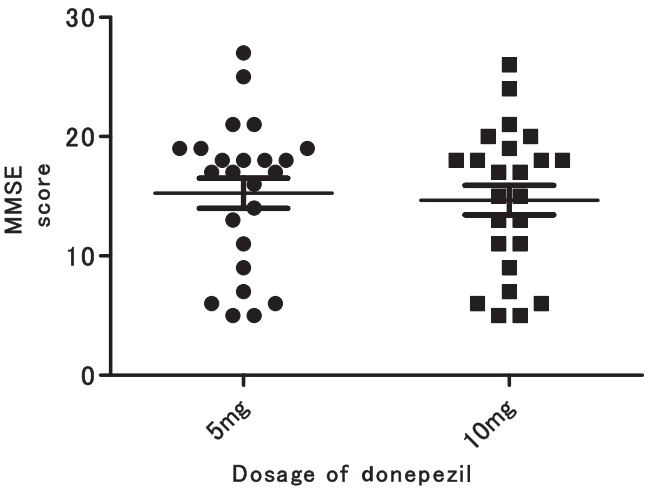

Figure 1 Changes in MMSE score after donepezil dosage was increased from 5 mg/day to 10 mg/day. After the dosage increase, the average MMSE score changed from 15.25 ± 6.24 to 14.67 ± 6.07; the difference in the score was not significant. MMSE, Mini-Mental State Examination.

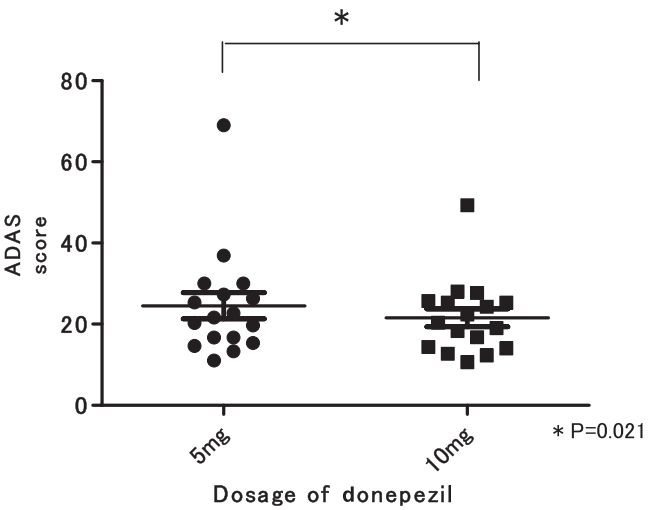

Figure 2 Changes in ADAS score after donepezil dosage was increased from 5 mg/day to 10 mg/day. After the dosage increase, the average ADAS score decreased from 24.52 ± 13.39 to 21.56 ± 9.14, and significant improvement was observed ($P = 0.021$). ADAS, Alzheimer's Disease Assessment Scale.

Table 2 Change in indicators of cerebral blood flow after a dosage increase of donepezil

	Donepezil 5 mg/day	Donepezil 10 mg/day
Severity (mean ± SD)	2.23 ± 1.26	2.13 ± 0.98
Extent (%) (mean ± SD)	40.76 ± 25.49	38.55 ± 25.39
Ratio (times) (mean ± SD)	2.94 ± 1.83	2.79 ± 1.98

There were no statistically significant differences in any indicator before and after the donepezil dosage increase.

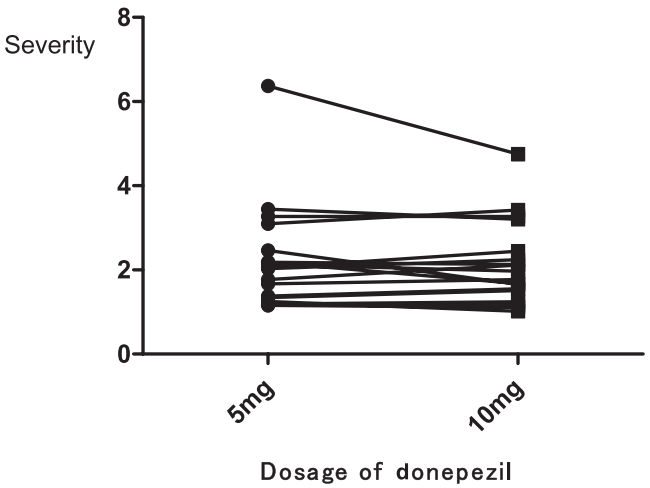

Figure 3 Change in severity after donepezil dosage was increased from 5 mg/day to 10 mg/day. After the dosage increase, severity (degree of decrease in blood flow in a specific region) decreased from 2.23 ± 1.26 to 2.13 ± 0.98.

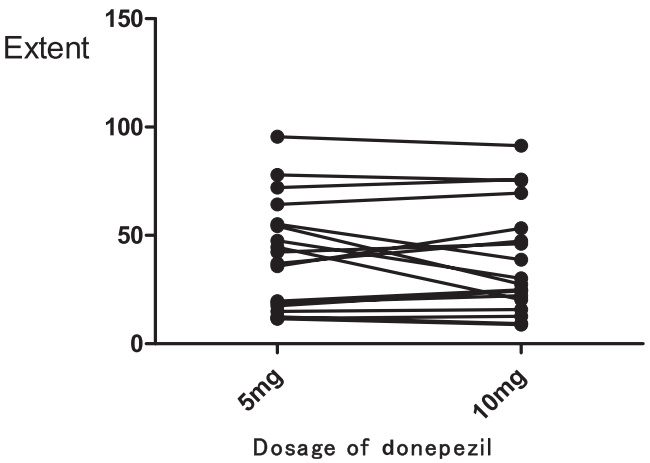

Figure 4 Change in extent donepezil dosage was increased from 5 mg/day to 10 mg/day. After the dosage increase, extent (proportion of the region demonstrating a decrease in blood flow of a specific region) decreased from 40.76 ± 25.49% to 38.55 ± 25.39%.

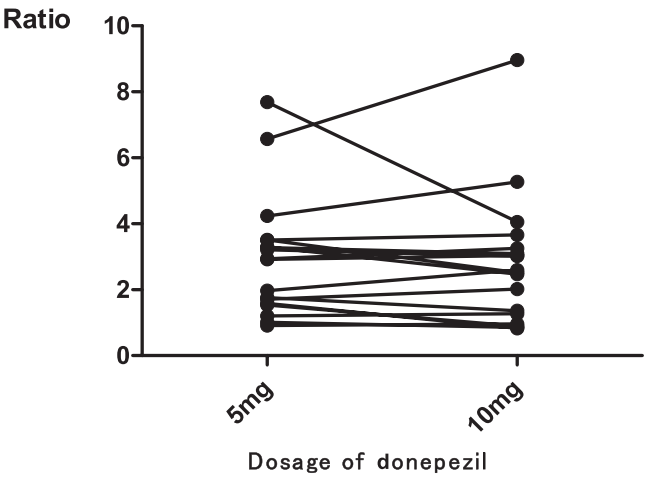

Figure 5 Change in ratio donepezil dosage was increased from 5 mg/day to 10 mg/day. After the dosage increase, ratio (ratio of decreases in blood flow between the entire brain and a specific region) decreased from 2.94 ± 1.83 to 2.79 ± 1.98 times.

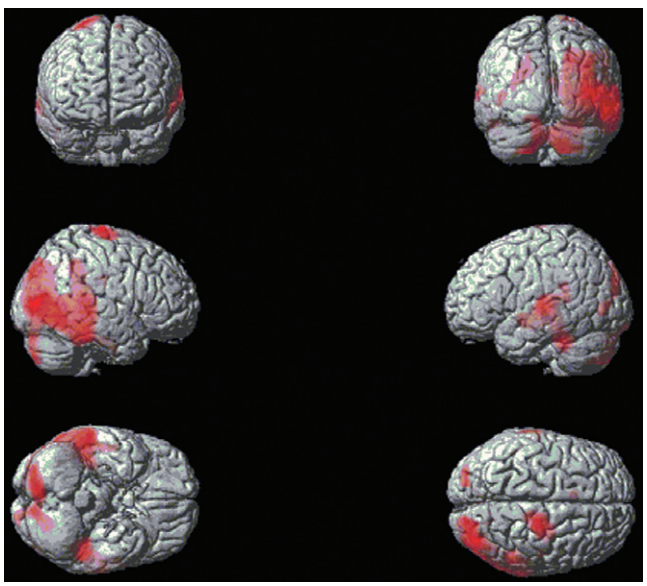

Figure 6 Region in significant increase of rCBF after donepezil dosage increase (n = 20, P < 0.05). Comparison of cerebral blood flow by SPM8 revealed significant increases in blood flow, after dosage increase to 10 mg/day, in the right occipital lobe, right temporal lobe, a portion of the left temporal lobe, right parietal lobe and bilateral posterior cerebellum (P < 0.05). rCBF, regional cerebral blood flow; SPM8, Statistical Parametric Mapping 8.

The relationships between carriers and non-carriers of ApoE4 and changes in dementia symptoms and CBF could not be determined.

DISCUSSION

Effect of high dosage of donepezil in neuropsychological testing

Internal administration of donepezil hydrochloride at 5 mg/day was approved for the treatment of mild to moderate AD in Japan in 1999, and its safety and efficacy have been established. Although this drug, which has an inhibitory effect on acetyl cholinesterase, improves the core symptoms of dementia within 38 weeks after initial administration, subsequent improvement has been reported to decrease.[7–9]

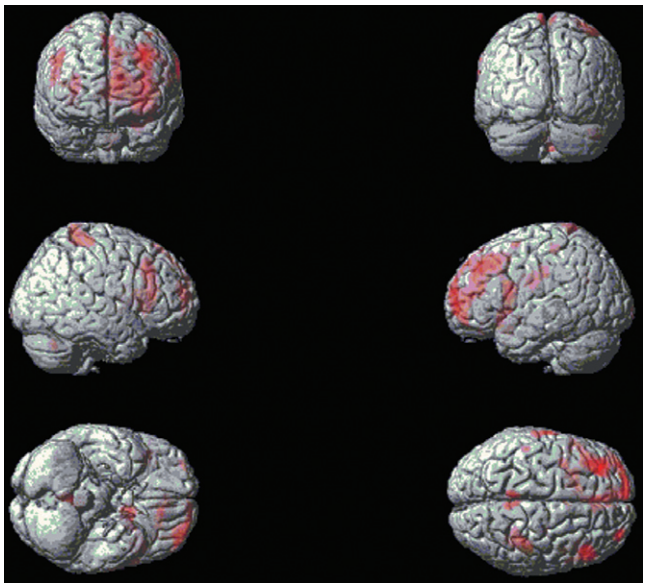

Figure 7 Region in significant decrease of rCBF after donepezil dosage increase ($n = 20$, $P < 0.05$). Comparison of cerebral blood flow by SPM8 revealed significant decreases in blood flow, after dosage increase to 10 mg/day, in the left frontal lobe, an extremely small portion of the right frontal lobe and a portion of the right parietal lobe ($P < 0.05$). rCBF, regional cerebral blood flow; SPM8, Statistical Parametric Mapping 8.

The use of 10-mg/day donepezil hydrochloride for the treatment of severe AD was approved in Japan in 2007. Nozawa *et al*. used MMSE and Revised Hasegawa Dementia Scale scores to compare cognitive function before and after donepezil hydrochloride dosage was increased to 10 mg/day in 61 Japanese AD patients. They reported that there were no significant changes in cognitive function at any time after the dosage was increased and that the higher dosage suppressed disease exacerbation.[10] In this study, although significant changes in MMSE scores were not observed after the dosage increase to 10 mg/day, significant changes in the ADAS-cog scores indicated a tendency for improvement.

ADAS-cog scores are determined based on lost points; a higher ADAS-cog score indicates increased exacerbation of cognitive function. The maximum possible score is 70 points; 10 points are assigned to memory recall, 12 to recognition, and 18 to orientation. Other parameters include oral language ability, language aural comprehension, aural comprehension of spontaneous speech, oral commands, object naming, constructional activity, conceptual exercises, and recognition ability of a presented text. The scores for these parameters are properly balanced, and this scale is considered suitable for observing changes in cognitive function involving drug intervention. The average MMSE score of the three excluded was significantly lower than that of the cases that completed the ADAS-cog test. This indicates that evaluation by ADAS is difficult in cases of advanced dementia.

The expression of ApoE4 phenotype is a risk factor for AD, and numerous related research findings have been reported.[11,12] Recently, ApoE4 was reported to be associated with the risk of AD onset as well as its long-term prognosis.[13] According to a study conducted by Nozawa *et al*., MMSE scores obtained after the increase in the donepezil hydrochloride dosage suggested exacerbation of cognitive function only in patients with expression of the ApoE4 phenotype.[10] However, no correlation was found between the expression of the ApoE4 phenotype and cognitive function or changes in CBF. This finding is attributable to the differences in the evaluation method, number of subjects, and observation period.

Adverse effects and dropout rate in this study

The dropout rate in a previous multicentre, placebo-controlled, double-blind study of advanced AD conducted in Japan was 13.5%,[14] which is not that different from the 16.7% of this study. With respect to adverse effects, the incidence of gastrointestinal symptoms (nausea) was lower in this study than in the previous study (4.2% vs 14.6%). This is thought to be attributable to the longer average duration of administration at 5 mg/day in this study than in the previous study (1111 days vs 4 weeks) before the dosage increase to 10 mg/day. In contrast, adverse effects in the form of psychological symptoms (e.g. lack of composure and increased excitation) were observed in 12.5% of subjects in this study while it occurred at a rate of 5.2% in the previous study. This increase is likely related to the small number of cases examined in this study, but regardless, when dosage is increased, caution is required concerning adverse effects associated with psychological symptoms.

Changes in CBF attributable to high dosage of donepezil

Based on differences in the three indicators of CBF defined by Matsuda *et al*., the relationship between the increased donepezil hydrochloride dosage and CBF was assessed with eZIS.[6] Values for the three

indicators, severity, extent, and ratio, decreased after the increase in the donepezil hydrochloride dosage, and although blood flow increase in the affected regions was suggested, no significant differences were observed. These findings indicate that these indicators are useful for the diagnosis of early AD but are not suitable for the diagnosis of severe AD. This may be attributed to the fact that in cases of severe AD, although the increase in the donepezil hydrochloride dosage cannot be expected to increase blood flow in the affected regions, there is a high likelihood that the increased dosage may increase the blood flow in other regions.

In addition, in drug intervention studies comparing the three indicators with eZIS analysis, the extent to which drug-induced increases in blood flow are reflected by the scores is unclear. However, meaningful results can be expected if the number of subjects is increased.

Comparison of CBF before and after the dosage increase was conducted with SPM8, and the sites at which CBF changed after the dosage increase were identified. SPM8 can help determine the sites at which significant changes in blood flow occur by statistically processing the sites on the basis of data from brain activation studies performed using PET and SPECT.[15] In this study, the sites at which CBF increased after the donepezil hydrochloride dosage was increased were the right occipital lobe, right temporal lobe, a portion of the left temporal lobe, right parietal lobe, and both sides of the posterior cerebellum, clearly indicating increased blood flow in the right brain. In contrast, the sites at which CBF decreased were the left frontal lobe, an extremely small portion of the right frontal lobe, and a portion of the right parietal lobe. As there were fewer sites with CBF decrease than increase, this finding was considered to be an indication of disease progression.

Correlating the sites at which blood flow increased with the improvement in symptoms is difficult. Since the changes in symptoms after the donepezil hydrochloride dosage increase included emotional changes, such as response when called by a caregiver, speaking of one's own volition, and a more cheerful expression, it is extremely interesting to consider a correlation with the sites in the right brain showing increased blood flow.

However, because donepezil hydrochloride caused this degree of change in the CBF, caution is required when a dosage increase is considered without ample thought of the risk of exacerbating behavioural and psychological symptoms of dementia, such as increased excitation, lack of composure, and irritability. Donepezil hydrochloride is effective against AD, and increasing the dosage from 5 mg/day to 10 mg/day was effective in the cases of advanced AD evaluated in this study. Although donepezil hydrochloride has also been reported to be effective against behavioural and psychological symptoms of dementia associated with AD,[16] it has been shown to exacerbate excitatory symptoms, highlighting the importance of increasing the dosage with due consideration to peripheral symptoms.

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