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Clinical efficacy and changes in the dosages of concomitantly used psychotropic drugs in memantine therapy in Alzheimer's disease with behavioral and psychological symptoms on dementia

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Abstract

Objective: We investigated the clinical efficacy and changes in the dosages of concomitantly used psychotropic drugs in memantine therapy in Alzheimer's disease (AD) with behavioral and psychological symptoms on dementia (BPSD).

Methods: The subjects were 38 inpatients who had been diagnosed with AD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). The outcome measures assessed were BPSD and cognitive function. BPSD was assessed using the neuropsychiatric inventory (NPI) and cognitive function was assessed using the mini-mental examination (MMSE). The changes in the dosages of concomitant psychotropic drugs were also assessed.

Results: Significant decreases were found in the memantine therapy group in the following NPI total score and five NPI subscales: delusions, hallucinations, agitation, irritability, and aberrant motor behavior, but no significant differences were seen between the memantine therapy group and the control group. Furthermore, the memantine therapy group allowed the dosage of the psychotropic drugs to be significantly reduced compared with the control group.

Conclusion: The results of this study suggest that the administration of memantine to patients with AD with BPSD may afford superior efficacy and may also make it possible to reduce the risperidone equivalent dose, the diazepam equivalent dose and the dosage of the psychotropic drugs.

Keywords: Alzheimer's disease, behavioral and psychological symptoms on dementia, memantine, psychotropic drugs

Introduction

Alzheimer's disease (AD) starts with marked memory and/or orientation impairment, and progresses to generalized cognitive dysfunction. During the course of the disease, behavioral and psychological symptoms of dementia (BPSD) are observed [Finkel *et al.* 1996]. BPSD are often a caregiving burden in patients with dementia. However, it has been pointed out that, as opposed to cognitive dysfunction, which progresses irreversibly and from which there is little chance of recovery, BPSD can be prevented or alleviated with appropriate interventions, changes in environment, drug therapy. When nondrug therapies are not effective, and there is substantial caregiver exhaustion, drug therapy with antipsychotics, antidepressants, benzodiazepines, anti-epileptic medications, etc., is offered.

Elderly patients generally have reduced liver and kidney function, are more susceptible to adverse drug reactions, and are more likely to experience a reduction in their activities of daily living (ADL) and in their quality of life (QOL) as a result of drug-induced adverse drug reactions. In elderly patients, the risk of drug-induced

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cognitive impairment increases as the number of concomitant drugs used increases [Obeso and Martinez-Lage 1987; Meltzer *et al.* 1998; Drimer *et al.* 2004; Stewart, 2005]. Consequently, in drug therapy in patients with AD accompanied by BPSD, efficacy should not be the sole objective; adverse drug reactions should be kept to a minimum, and the number of concomitant drugs should be reduced as much as possible to avoid complicated dosing regimens.

Against this background, memantine hydrochloride, a therapeutic medication for AD that antagonizes N-methyl-D-aspartate (NMDA) receptors, a subtype of glutamic acid receptors, has been reported to be effective against BPSD in clinical studies [Gauthier *et al.* 2008]. However, there have been almost no reports that have looked at the clinical efficacy in BPSD and the changes in the dosages of concomitant psychotropic drugs in memantine therapy in AD accompanied by BPSD in Japan. In this study, therefore, we investigated the clinical efficacy and the changes in the dosages of concomitant psychotropic drugs following 16 weeks of memantine therapy relative to baseline in patients with AD accompanied by BPSD.

Methods

Subjects

The subjects were 38 patients who were being treated on an inpatient basis at the psychiatry departments of Tanzawa Hospital or home for the elderly Adachi Shinseien and had been diagnosed with AD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV); patients were also diagnosed with probable AD according to the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [McKhann *et al.* 1984]. AD patients with BPSD receiving psychotropic drugs were enrolled into this study. Inclusion criteria were: patients were not concomitantly receiving cholinesterase inhibitors; patients had been treated with a stable dose of psychotropic drugs for at least 2 months. Memantine is excreted renally. Patients with renal impairment were therefore excluded from this study. The memantine therapy group and the control group were recruited separately. In addition, a group of AD patients (20 subjects) was established as a control group who continued receiving psychotropic drugs, and whose background characteristics were consistent with those of the patients in the group that received memantine (18 subjects). The patients were receiving psychotropic drugs before they received memantine.

Furthermore, all of the subjects who participated in this study were inpatients whose treatment compliance had been confirmed each time by nurse or caregiver, and whose treatment compliance was thus assured. They were required to be symptomatically stable, as judged by the treating psychiatrist, to be able to complete all of the clinical measures.

The study was an open-labeled, flexible-dose, naturalistic observational trial of AD patients undergoing the usual care and who required a change in their medication because of persistent symptoms or troublesome side effects. The control group had persistent symptoms or side effects. Patients had high scores in the neuropsychiatric inventory (NPI), even though they were considered stable. However, there patients could not be considered refractory to psychotropic drugs.

Only patients or family (caregivers) who had provided voluntary informed consent in writing to participate in this study upon receiving a full explanation of the purpose and method of the study were enrolled, while patient confidentiality was afforded all due consideration, as were ethical considerations.

Therapy method

Subjects received memantine in addition to their previous therapeutic medications. Subjects were given an initial dose of memantine 5 mg in addition to their previous therapeutic medications, and the memantine dose was increased by 5 mg increments at 2-week intervals in consideration of safety. After 6 weeks, the memantine dosage was increased as necessary to optimize the dose, and wherever possible the dosages of psychotropic drugs were reduced. Subjects were prescribed memantine within the dose range of 10–20 mg/day. The psychotropic equivalents calculation table of Inagaki and Inada was used as a guideline for calculating psychotropic equivalents [Inagaki and Inada, 2006, 2012] when calculating the baseline to postdose changes in the dosages of the concomitant psychotropic drugs,

Table 1. Subject characteristics.

Characteristics	Control group (*n*=20)	Memantine therapy group (*n*=18)	*p*-value
Age (years) (mean ± SD)	83.4 ± 7.2	83.6 ± 10.0	0.94
Gender (M:F)	4 : 16	2 : 16	
Duration of illness (years) (mean ± SD)	7.2 ± 3.1	8.6 ± 3.1	0.16
Risperidone equivalents dose (mg/day) (baseline)(mean ± SD)	0.8 ± 0.9	0.4 ± 0.7	0.15
Diazepam equivalents dose (mg/day) (baseline) (mean ± SD)	2.0 ± 3.0	1.4 ± 2.3	0.51
Sodium valproate dose (mg/day) (baseline) (mean ± SD)	120.0 ± 176.5	83.3 ± 98.5	0.44
MMSE score (baseline) (mean ± SD)	3.7 ± 8.0	3.5 ± 4.3	0.92
NPI total score (baseline) (mean ± SD)	36.8 ± 13.8	38.6 ± 11.3	0.67

Value are mean ± SD or *n*. MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; SD, standard deviation.

and the subjects' daily dosages were calculated in terms of risperidone or diazepam equivalents.

Assessment methods

The following clinical assessments were performed both at baseline and at 16 weeks by the psychiatrist who was providing the actual therapy. The outcome measures assessed were BPSD and cognitive function. BPSD was assessed using the NPI [Cummings *et al.* 1994] and cognitive function was assessed using the mini-mental examination (MMSE) [Folstein *et al.* 1975].

Statistical analysis

The Wilcoxon signed rank sum test was used to analyze efficacy and changes in the dosages of concomitantly used psychotropic drugs in memantine therapy. The Wilcoxon signed rank sum test was also used to analyze differences between the memantine therapy group and the control group in terms of efficacy or changes in the dosages of concomitant psychotropic drugs. The significance level was set at $p < 0.05$ for each.

Results

No significant differences were seen between the memantine therapy group and the control group in the baseline NPI total score, the baseline MMSE score, the mean daily dose of the previous treatment drug, the mean duration of illness, or the mean age of the patients (Table 1). The mean dosage of memantine at the endpoint was 16.5 ± 4.6 (mg/day). None of the patients had withdrawn due to psychiatric symptom worsening, adverse reactions, or worsening adherence.

Significant decreases were found in the memantine therapy group in the following NPI total score and five NPI subscales: delusions, hallucinations, agitation, irritability, and aberrant motor behavior, but no significant differences were seen between the memantine therapy group and the control group (Table 2). On the other hand, no changes in the MMSE score were found either in the memantine therapy group or the control group (Table 2). The mean changes from baseline in the risperidone equivalent dose, the diazepam equivalent dose, and the dosage of sodium valproate were significantly higher in the memantine therapy group than in the control group (Table 3).

Discussion

No differences were seen in efficacy in the improvement of BPSD between the memantine therapy group and the control group when inpatients with AD were given memantine for 16 weeks, and the efficacy thereof with respect to BPSD was compared with that obtained in the control group, which continued to receive psychotropic drugs. Significant decreases were found in the memantine therapy group in the following five NPI subscales: delusions, hallucinations, agitation, irritability, and aberrant motor behavior.

Table 2. Clinical efficacy.

	Control group (*n*=20)				Memantine therapy group (*n*=18)				*p*-value
	Baseline		Change from baseline to 16 weeks		Baseline		Change from baseline to 16 weeks		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
NPI									
Total	36.8	13.8	−8.8	6.3*	38.6	11.3	−11.4	6.9*	0.24
Delusions	2.1	3.0	−0.8*	1.3*	1.9	3.1	−0.8*	1.2*	0.98
Hallucinations	4.8	2.7	−1.5	1.6*	3.9	3.8	−1.8	2.0*	0.61
Agitation	7.5	4.3	−2.3	2.1*	7.4	3.4	−3.3	2.4*	0.18
Depression	0.1	0.2	–	–	0.1	0.2	–	–	–
Anxiety	3.1	3.6	−0.6	1.3	2.1	3.2	−0.6*	1.5*	0.87
Euphoria	1.2	3.2	−0.3	1.5	0.5	1.9	–	–	0.19
Apathy	6.7	2.9	–	–	6.7	2.7	–	–	–
Disinhibition	0.4	1.8	–	–	1.8	3.3	−0.7	1.6	0.09
Irritability	7.4	4.2	−4.9	3.3*	6.9	3.9	−3.1	2.4*	0.06
Aberrant motor behavior	3.2	3.9	−0.8*	1.5*	7.6	3.5	−1.2*	1.6*	0.47
MMSE score	3.7	8.0	–	–	3.5	4.3	–	–	–

Values are mean ± SD. MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; SD, standard deviation.
*$p < 0.005$ *versus* baseline, **$p < 0.05$ *versus* baseline

Table 3. The change over time in the risperidone equivalent dose, the diazepam equivalent dose and the sodium valproate dose.

	Control group (*n*=20)				Memantine therapy group (*n*=18)				*p*-value
	Baseline		Change from baseline to 24 weeks		Baseline		Change from baseline to 24 weeks		
Risperidone equivalent dose (mg/day)	0.8	0.9	0.1	0.1	0.4	0.7	−0.2	0.4*	0.0036
Diazepam equivalent dose (mg/day)	2.0	3.0	−0.1	0.6	1.4	2.3	−1.1	1.5*	0.0012
Sodium valproate dose (mg/day)	120.0	176.5	–	–	83.3	98.5	−38.9	60.8*	0.0069

*Significant difference was found by Wilcoxon signed-rank test ($p < 0.05$).
Mean ± standard deviation.

Our findings are therefore consistent with the results of the clinical studies that have been conducted to date [Cummings *et al.* 2006; Gauthier *et al.* 2008]. Although there have been reports of the concomitant use of memantine and cholinesterase inhibitors being effective against BPSD [Clerici *et al.* 2011; Cummings *et al.* 2006], it appears that, in this study, the fundamental effects of memantine on BPSD were obtained in memantine monotherapy. As far as the effects on cognitive function, a secondary outcome measure in this study, were concerned, as in the control group, no changes were found in the MMSE score. The reason that our findings were different than those of overseas clinical studies [Reisberg *et al.* 2003; Tariot *et al.* 2004] is believed to be that our study was conducted in patients with severe AD with MMSE scores of 5 or below at baseline,

and was not used that the Severe Impairment Battery (SIB) would have been a more sensitive cognitive scale than the MMSE for that level of severity of dementia. When BPSD accompany severe AD, this frequently results in a considerable caregiving burden, appreciably complicates treatment and care, and leads to drug therapy with, for example, antipsychotic medications.

Since elderly patients generally have reduced liver and kidney function and are thus more susceptible to adverse drug reactions, every effort must be made to reduce the dosing levels that are used in the elderly. In 2005, the Food and Drug Administration (FDA) reported effects including an increased death rate with new antipsychotic medications in elderly patients, and also reported similar results with conventional antipsychotic medications; in elderly patients, therefore, caution must be exercised when initiating drug therapy [Kudo, 2012]. The results of this study suggest that the use of memantine may result in a significant decrease in the risperidone equivalent dose compared with patients not receiving memantine, which would result in at least a certain degree of improvement in safety. Particularly in elderly patients, benzodiazepine is known to impair cognitive function, and elderly patients being given benzodiazepine must be watched carefully for signs of delirium [Inoue *et al.* 2011]. The results of this study suggest that the use of memantine may result in a significant decrease relative to patients not receiving memantine in the equivalent dose of diazepam, which results in cognitive impairment. As defined by the International Psychogeriatric Association (IPA), BPSD are symptoms of dementia. Therefore, BPSD should be controlled using therapeutic medications for dementia, rather than off-label drugs. The findings of this study are consistent with this position.

Limitations

This study had a relatively small sample size, and was a short-term study (16 weeks), and was furthermore an open-label, not a double-blind, study, so the possibility that bias was introduced into the results cannot be ruled out, and there are consequently limits to the conclusions that can be drawn from this study. A double-blind, randomized, controlled study in the AD subjects with BPSD may be necessary in the future in order to clarify the efficacy and the changes in the dosages of concomitant psychotropic drugs of memantine.

Conclusion

The results of this study suggest that the administration of memantine to patients with AD with BPSD may afford superior efficacy and may also make it possible to reduce the dosage of the psychotropic drugs.

Conflict of interest statement

Dr Suzuki received honoraria from Janssen, Otsuka, and Dainippon Sumitomo. Dr Inoue received honoraria from Eisai. Dr Nishiyama received honoraria from GlaxoSmithKline. Dr Mikami received a grant from Tokai University, Kanagawa, Japan, and honoraria from Janssen, Astellas, Otsuka, Yoshitomiyakuhin, Shionogi, and Kanagawa Prefecture Medical Association. Dr Gen received honoraria from Janssen.

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