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Efficacy of perospirone in the management of aggressive behavior associated with dementia

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Abstract

We assessed the efficacy of the serotonin dopamine antagonist, perospirone (PER) on aggressive and agitated behavior in demented patients. Eighteen outpatients with dementia diagnosed according to the DSM-IV were enrolled in this study, and their behavioral symptoms and cognitive impairments were assessed with the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) and Mini-Mental State Examination (MMSE) instruments for a period of 6 weeks. The maximum benefit of PER was achieved at a mean dose of 7.4 mg/day. Post-hoc analysis showed significant improvement in verbal outbursts after 4 weeks and in agitation scores after 4 and 6 weeks. Only 2 patients dropped out of the study, because of adverse effects, and no serious adverse effect was observed. The data suggest that PER is effective in improving aggressive and agitated behavioral symptoms in demented patients and that it is safe to use in elderly patients.

Keywords: Aggressive behavior; Behavioral and psychological symptoms of dementia; Dementia; Perospirone

1. Introduction

The behavioral and psychological symptoms of dementia (BPSD), which include aggression, agitation, screaming, wandering, hallucination, and delusion, have a negative impact on patients' activities of daily living and on caregivers' quality of life. Among the BPSD, aggression and agitation are especially serious and problematic symptoms for family caregivers, and these symptoms are often the primary cause of hospital admission or institutional care (American Psychiatric Association, 1997; Schneider et al., 1996). In addition, it is reported that aggression and agitation occur in about 20–80% of patients with Alzheimer's disease (AD) (Burns et al., 1990; Cooper et al., 1990; Lyketsos et al., 2000; Mega et al., 1996), and that patients with vascular dementia (VD) also often exhibit aggression and agitation (Cohen et al., 1993).

Although non-pharmacological interventions, such as the verbal environmental intervention, should be first-line for milder BPSD (American Psychiatric Association, 1997; Asada et al., 2000), many psychotropic agents (e.g. conventional antipsychotics, benzodiazepines, antidepressants, anticonvulsants, and beta-blockers) have been used to manage aggressive behavior. However, their efficacy is insufficient (Cohen et al., 1993; Schneider et al., 1996) and their use has been limited because of adverse effects such as orthostatic hypotension, arrhythmia, extrapyramidal symptoms (EPS), urinary retention, constipation, sedation, and delirium (Brodaty et al., 2003; De Deyn et al., 1999; Katz et al., 1990; Schneider et al., 1996). Recently, newer atypical antipsychotics, characterized by the serotonin (5-HT2) and dopamine (D2) antagonists, have been used for the treatment of aggression in demented patients. Double-blind, placebo-controlled trials have demonstrated that

Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease; BPSD, behavioral and psychological symptoms of dementia; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EPS, extrapyramidal symptoms; MMSE, Mini-Mental State Examination; VD, vascular dementia.

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some atypical neuroleptics, such as risperidone and olanzapine, have beneficial effects and are well tolerated (American Psychiatric Association, 1997; Brodaty et al., 2003; De Deyn et al., 1999; Schneider et al., 1996; Street et al., 2000) in the treatment of aggression and agitation in demented patients.

Perospirone(*cis*-*N*-[4-[4-(1,2-benzisothiazole-3-yl)-1-piperazinyl]butyl]cyclohexane-1,2-dicarboximide monohydrochloride) (PER) is a novel antipsychotic agent available in Japan for the treatment of schizophrenia. PER has a unique pharmacologic profile and acts as a serotonin-dopamine antagonist (Onrust and McClellan, 2001) as well as a partial serotonin (5-HT1A) agonist (de Paulis, 2002). Buspirone, which exhibits 5-HT1A agonist effects, has been reported to be effective in the treatment of aggressive and agitated behaviors associated with dementia (Cantillon et al., 1996; Hermann and Eryavec, 1993; Sakauye et al., 1993). Previous studies demonstrating buspirone efficacy led us to hypothesize that PER would be effective and safe in the treatment of aggressive and agitated behaviors in patients with dementia. We previously reported six patients with dementia, in whom PER reduced aggression (Sato et al., 2006). This article further presents the effects of PER on aggressive and agitated behaviors associated with dementia.

2. Methods

2.1. Patient population

A consecutive series of 18 patients were enrolled in this study. All patients were referred to the outpatient clinic of Ishizaki Hospital between April 2003 and March 2004. Eligibility criteria for the present study were: meeting the diagnosis of dementia of the Alzheimer's type (AD) or vascular type (VD) according to DSM-IV (American Psychiatric Association, 1994); and exhibiting moderate to severe agitation or aggressive behavior requiring pharmacotherapy for at least 1 month. This study protocol was approved by the Internal Review Board of Ishizaki Hospital. Patients and their caregivers provided written informed consent for study participation. However, if the patient was lack of ability to give it, we obtained it from only their caregivers. The patients underwent physical, neurologic, and laboratory examinations as well as brain magnetic resonance imaging. If they had a serious physical illness or a past history of mental disorders, they were excluded from the study.

2.2. Drug administration

Initially, the administration of PER started at 8 mg/day divided into morning and evening doses. If efficacy was deemed insufficient, the dose was increased weekly by 4 mg/day. However, if the initial dosage of PER was associated with any adverse effects, the dose was decreased weekly by 2 or 4 mg/day. The maximum effective dose was determined based on clinical judgment and the BEHAVE-AD scores.

Basically, the patients treated with PER monotherapy during the study period. However, 9 cases had previously received other medications (sodium valproate 6 cases, tiapride 4 cases, donepezil 3 cases, risperidone 1 case, olanzapine 1 case). In these cases, risperidone and olanzapine were discontinued, while the other previous medications were continued, and their dosage was unchanged during the study.

2.3. Study design and assessment instruments

The patients were assessed four times, at baseline and at 2, 4 and 6 weeks after the start of PER administration. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Clinical Dementia Rating (CDR) (Hughes et al., 1982) were used to assess the severity of cognitive deficits. Psychiatric and behavioral symptoms were evaluated with the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) instrument (Reisberg et al., 1987). The BEHAVE-AD scale measures behavioral disturbances in the seven major categories of "paranoid and delusional ideation," "hallucination," "activity disturbances," "aggressiveness," "diurnal rhythm disturbances," "affective disturbances," and "anxieties and phobias." In this study, the change in the total score and aggressiveness score including "verbal outbursts," "physical threats and violence," and "agitation" subscales of the BEHAVE-AD were evaluated.

2.4. Data analysis

Initial and end-point MMSE scores were compared using the Wilcoxon signed-rank test. Changes in the total BEHAVE-AD scores and each subscale of BEHAVE-AD at each time point were analyzed by means of repeated-measures analysis of variance (ANOVA). Dunnett test was used for Post-hoc analysis of ANOVA comparing baseline and 2, 4 and 6 weeks after scores. The significant level was set at $p<0.05$.

3. Results

The 6-week course of treatment was completed by 16 patients (88.9%); and 2 patients discontinued PER due to adverse effects. Table 1 shows the background characteristics of

Table 1
Demographic characteristics of 18 patients

	Variable
Age (years, mean±SD) (range)	78.1±6.6 (65–89)
Sex	
Male	7
Female	11
Diagnosis	
AD	15
VD	3
MMSE (mean±SD)*	
Baseline	12.3±6.3
End-point ($n=16$)	15.6±8.9
CDR (mean±SD)	2.2±0.4
Perospirone dose (mg/day, mean±SD) (range) ($n=16$)	7.4±3.5 (2–12)

AD: Alzheimer's disease.
VD: vascular dementia.
MMSE: Mini-Mental State Examination.
CDR: Clinical Dementia Rating.
* Not significant, Wilcoxon signed-rank test.