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Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia

D. Aarsland[1]*, M. Hutchinson[2] and J. P. Larsen[3]

[1]*Section of Geriatric Psychiatry, Rogaland Central Hospital, Stavanger, Norway*
[2]*Department of Neurology, New York University School of Medicine, New York, USA*
[3]*Department of Neurology, Rogaland Central Hospital, Stavanger, Norway*

SUMMARY

Background Cholinesterase inhibitors with additional nicotinic activity, such as galantamine, may be useful in PD patients with dementia (PDD) since stimulation of nicotinic receptors may prevent the down-regulation that is likely to accompany cholinesterase inhibition and facilitate dopamine release in the striatum.
Methods Sixteen PDD patients (six female) with onset of cognitive impairment after at least one year with parkinsonism participated in this open-label trial of galantamine. Cognitive, psychiatric, and motor symptoms were assessed before and after 8 weeks of treatment with galantamine using unstructured clinical assessment as well as rating scales including the Mini-Mental State Examination (MMSE), clock drawing test, verbal fluency and selected items from the Neuropsychiatric Inventory (NPI).
Results Age (mean, SD) was 75.6 (5.2) years, duration of PD 13.4 (5.9), duration of dementia 2.1 (1.7) years, Hoehn and Yahr score was 3.8 (0.8) and baseline MMSE score was 17.7 (6.7). Side-effects caused discontinuation in three patients, but were rare and mild in the remaining 13. Improvement of global mental symptoms was noted in eight patients, whereas worsening was reported in four. Hallucinations improved in seven of the nine patients with hallucinations before treatment. Parkinsonism improved in six patients, but a mild worsening of tremor was noted in three. Clock-drawing improved ($p = 0.016$), and trends towards improvement on MMSE ($p = 0.09$) and verbal fluency ($p = 0.16$) were found.
Conclusions Although controlled trials are needed, the findings suggest that galantamine is useful in patients with PDD.

KEY WORDS — Parkinson's disease; dementia; cholinesterase inhibitor; galantamine; hallucinations; cognition

INTRODUCTION

Dementia eventually develops in nearly 80% of patients with Parkinson's disease (PD) (Aarsland *et al*., 2003) and has important clinical consequences with regard to increased mortality, increased caregiver burden and increased risk of admission to nursing home (Aarsland *et al*., 1999; Aarsland *et al.*, 2000). The underlying mechanisms for dementia in PD are not known in detail, but Alzheimer-type changes, although less prominent than in Alzheimer's disease (AD), and cortical Lewy bodies may contribute (Jellinger, 1999). However it appears increasingly likely that in PD patients, the cholinergic deficit, which is of similar severity as in dementia with Lewy bodies (DLB) and may be greater than that associated with AD (Perry *et al*., 1993; Tiraboschi *et al*., 2000), contributes substantially to dementia. Cholinergic deficits are more marked in PD patients with dementia compared to without (Kuhl *et al*., 1996), and are associated with hallucinations in DLB (Perry *et al*., 1999). Furthermore, due to secondary up-regulation of cortical muscarinic receptors, cortical cholinoceptive neurons are more intact in PD than in AD (Perry *et al*., 1993). This, in combination with less neurofibrillary tangles and neuronal death, suggest that cholinergic therapy may more effectively improve cognition and hallucinations in PD than in AD patients. This hypothesis was supported by an

*Correspondence to: Dr D. Aarsland, Section of Geriatric Psychiatry, Rogaland Central Hospital, Armauer Hansensvei 20, P.O. Box 1163 Hillevåg, 4095 Stavanger, Norway.
Tel: 47 51 51 51 51. Fax: 47 51 51 50 75. E-mail: daa@sir.no

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open-label report with tacrine (Hutchinson and Fazzini, 1996). In one recent placebo-controlled study with donepezil (Aarsland *et al*., 2002) and open-label reports with rivastigmine (Reading *et al*., 2001) improvement of cognition in PD patients with dementia was reported.

Results from a wide range of studies suggest that the nicotinic receptors may be a therapeutic target in PD patients with dementia. Firstly, there are important functional interactions of cholinergic nicotinic receptors and dopaminergic neurons in striatal and thalamic nuclei. For instance, nicotinic receptors are located on presynaptic dopamine terminals and may facilitate dopamine release in the striatum (Perry *et al*., 1998; Giorguieff *et al*., 1977). Secondly, reduction in cortical nicotinic receptor binding has been found in PD, and this parallels the degree of dementia (Perry *et al*., 1993; Whitehouse *et al*., 1983) and seems to be related to visual hallucinations and cognitive fluctuations in Lewy body disease (Ballard *et al*., 2002a). Thirdly, nicotinic stimulation may improve cognition, attention, arousal, processing speed and motor symptoms in PD patients (Rusted *et al*., 2000). Finally, smoking is inversely associated with the risk of PD (Allam *et al*., 2003). Thus, galantamine, a cholinesterase inhibitor which also potentiates cholinergic nicotinic neurotransmission by allosterically modulating nicotinic acetylcholine receptors, and which improves cognition in AD (Tariot *et al*., 2000), may be particularly useful in patients with PD. To address this question, we performed an open-label trial in patients with PD and dementia at two centres in Norway and US for 8 weeks and evaluated the effects on cognition, psychiatric symptoms and parkinsonism.

PATIENTS AND METHODS

Patient selection

Consecutive patients referred to the outpatient Neurological and Psychogeriatric clinics in Stavanger, Norway, and to the Department of Neurology, New York, US were included. The diagnosis of PD was made by a neurologist according to explicit criteria based on the UK Brain Bank (Daniel and Less, 1993). Patients were included if the DSM-IV-criteria for Dementia due to PD (American Psychiatric Press, 1994) were fulfilled after a clinical interview of the patient and a caregiver as well a neuropsychiatric examination performed by a psychiatrist (DA) or neurologist (MH). In order to avoid inclusion of patients with DLB, duration from onset of PD until development of cognitive impairment or hallucination had to be at least one year (McKeith *et al*., 1996). Cognitive impairment had to be substantiated with a Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975). A caregiver (usually a spouse for home-dwelling and a nurse or nurse assistant for institutionalised patients) had to be available and to assist with data collection. Patients were not included if they had active, severe physical disease other than PD or other conditions that could account for the neuropsychiatric symptoms, received anticholinergic drugs or other drugs which might cause cognitive impairment or worsening of parkinsonism, including tricyclic antidepressant and typical antipsychotic agents. A washout period of at least one week before baseline assessment was mandatory if such drugs were used.

Procedures

The patients and family members provided informed consent after the study protocol had been explained for them. A physical examination was performed at baseline, including routine laboratory tests and brain imaging (CT or MRI), and parkinsonism was staged using the Hoehn and Yahr stage (Hoehn and Yahr, 1967). The initial dose was galantamine 4 mg bid, and after 4 weeks the dose was increased to 8 mg bid. Patients were evaluated before treatment and after 8 weeks of treatment. Antiparkinson-medication remained stable during the treatment period.

Outcome measures

The primary outcome variables were global ratings (improved, no change, or worse) of cognition, hallucinations, and parkinsonism based on direct observation of patient and a clinical interview of patient and the caregiver by a neurologist (MH) or a psychiatrist (DA). The MMSE was administered before and after treatment to assess the change in cognitive performance. A change of 3 points or more was considered clinically significant (Clark *et al*., 1999). The delusion and hallucination items of the Neuropsychiatric Inventory (Cummings *et al*., 1994), the verbal fluency measure of the Dementia Ratings Scale (shopping list; Mattis, 1975), and the clock drawing test (Manos *et al*., 2001) were administered to the Norwegian sample. Wilcoxon rank sum test was used to compare performance before and after treatment.

Patients and caregivers were questioned whether side-effects, including those typical for treatment with cholinesterase inhibitors, such as nausea, vomiting, anorexia, headache or other symptoms had occurred during the treatment period.

RESULTS

Sixteen subjects (six female) were included, 11 from Norway and five from the US. Mean age (SD) was 75.6 (5.2) years, duration of PD 13.4 (5.9) and of dementia 2.1 (1.7) years, MMSE score was 17.7 (6.7) and Hoehn and Yahr score 3.8 (0.8). All patients were taking levodopa, and one also received a dopamine agonist. Five were on stable and low-dose treatment with an atypical antipsychotic agent (olanzapine, quetiapine or clozapine). Three patients withdrew prematurely due to adverse events: one developed vomiting after 3 days which recurred when he was restarted. Another was withdrawn after a week because of worsening tremor. Another was withdrawn after 4 weeks due to anorexia, nausea, and vomiting. Of the completers, three had mild gastrointestinal side-effects, one had sedation, and one head-ache. Only the 13 patients who completed 8 weeks of treatment are included in the further analyses.

The global clinical changes on cognition, hallucinations and parkinsonism are summarised in Table 1. Cognition improved in eight (62%) patients. In four (31%) patients a decline was noted. Hallucinations improved in seven of the nine patients (78%) with hallucinations at baseline. In three of these patients, who had marked symptoms before treatment (i.e. NPI hallucination score 6), the hallucinations disappeared completely. One patient without hallucinations at baseline developed marked symptoms (i.e. NPI hallucination score of 6) during treatment. Parkinsonism improved in six patients (46%). In three (23%) patients, worsening of parkinsonism occurred. The clinical notes suggest that the worsening was mild and mainly included worsening of tremor, whereas three of those who improved showed marked improvement, substantiated by the Hoehn and Yahr stage which improved from 4 to 2 in two of these patients.

Mean MMSE score improved from 18.5 (SD 7.1) to 20.8 (5.4) ($z = 1.7$, $p = 0.09$). Six (46%) patients improved 3 points or more (four of these improved 4-points or more), whereas one patient worsened three and one 4 points. There was no association between baseline score and improvement on the MMSE (Mann–Whitney $U = 19.0$, $p = 0.8$). Improved performance was found on the clock drawing test ($n = 8$) ($z = 2.4$, $p = 0.016$), and a non-significant trend on verbal fluency ($n = 9$) ($z = 1.4$, $p = 0.15$) was found.

Table 1. Global clinical change and change on the MMSE

	Improved	No change	Worse
Cognition	8	1	4
Hallucinations*	7	1	1
Parkinsonism	6	4	3
MMSE#	6	5	2

The numbers represent number of patients among the 13 completers.
*$n = 9$ completers with hallucinations at baseline.
± 3 or more points represent significant change (Clark *et al.*, 1999).

A case history

A 76 year old man diagnosed with PD 20 years ago had developed severe dementia during the previous four years. Fluctuations of consciousness, visual hallucinations, agitation, and depression were present. He was unable to walk without support from two persons, eat, dress or help himself during toileting. NPI score 66. He had severe hypophonia, akinesia and rigidity, and the Hoehn and Yahr scale was 5. He was unable to perform formal cognitive testing. He knew his age but was unable to remember other personal or situational information.

After eight weeks of treatment with galantamine, he was able to walk with mild support, was attentive, smiling, and able to talk and respond adequately. His MMSE score was 15. According to his assistant nurse and his wife, improvement began after one week of galantamine treatment. Feeding and toileting, mood, hallucinations and communication skills had improved markedly. He fell less often, was more awake during the day, less agitated, and had less fluctuating consciousness. His NPI score was 7, and the Hoehn and Yahr was stage 4.

DISCUSSION

These findings suggest that treatment with galantamine can improve cognition, hallucinations and even motor symptoms in patients with PD and dementia. Clinically meaningful improvement of cognition occurred in 64% of the patients. The mean MMSE improvement of 2.3 points is comparable to that reported after treatment with other cholinesterase inhibitors in PD and dementia (Reading *et al.*, 2001; Aarsland *et al.*, 2002), although less pronounced than previously reported on tacrine in PD (Hutchinson and Fazzini, 1996). However, 46% of the completers improved 3 points or more on the MMSE, an improvement suggested to be clinically meaningful (Clark *et al.*, 1999). Hallucinations, a common symptom with important consequences for caregivers (Aarsland *et al.*, 1999) and risk for nursing home

placement (Aarsland *et al.*, 2000), improved in the majority of patients with pre-treatment hallucinations, and a complete remission was seen in some of these patients. Motor improvement was found in 40% of patients, and was substantial in some of these patients, although in some patients a mild worsening of parkinsonism was observed. Thus, although some patients with PD did not respond or got worse on treatment with galantamine, a subgroup of PD seem to have a marked clinical improvement.

Since this was an open-label study, the possibility of placebo effects influencing the results cannot be excluded. In addition, fluctuating cognition in PD patients with dementia (Ballard *et al.*, 2002b) could also influence the cognitive performance. Large, placebo-controlled trials are needed to confirm the positive findings of this and other preliminary findings of cholinesterase inhibitors in PD.

We speculate that the effects of cholinesterase inhibition in PD patients with dementia may be augmented by additional nicotinic activity. Such stimulation may prevent the down-regulation of such receptors in the presence of cholinesterase inhibitors. These receptors are not restricted to the cortex but are also located in the striatum as well, facilitating presynaptic dopamine release. This hypothesis is also supported by the marked improvement on tacrine (Hutchinson and Fazzini, 1996), which also has marked nicotinic activity (Hellstrom-Lindahl *et al.*, 2000). Finally, cholinergic activity in the thalamus, mediated by both muscarinic and nicotinic receptors, is though to be of importance in the regulation of sleep and wakefulness (Perry *et al.*, 1999), a mechanism which is severely disturbed in many PD patients (Gjerstad *et al.*, 2002). Possibly, the dual effect of galantamine contributes to increased attention and wakefulness, which could cause improved cognitive performance.

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