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RIVASTIGMINE IN THE TREATMENT OF DEMENTIA WITH LEWY BODIES: PRELIMINARY FINDINGS FROM AN OPEN TRIAL

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ABSTRACT

The objective of this study was to assess the tolerability and efficacy of rivastigmine in a group of patients with probable dementia with Lewy bodies (DLB), using an open label study. Open label treatment was with rivastigmine up to maximum tolerated dose (mean 9.6 mg daily, range 3–12 mg). Eleven patients with DLB, mean age 78.5 years, were treated with this cholinesterase inhibitor. After 12 weeks of treatment, mean Neuropsychiatric Inventory scores fell by 73% for delusions, 63% for apathy, 45% for agitation and 27% for hallucinations. Five of the patients (45%) experienced very significant clinical improvements that had not been achieved with other treatments, including low dose neuroleptics. Medication was well tolerated and parkinsonian symptoms tended to improve. Cholinesterase inhibition may be a safe and effective alternative to neuroleptic treatment in DLB. Such effects may also prove to be applicable to the management of neuropsychiatric symptoms in Parkinson's disease and Alzheimer's disease.

KEY WORDS—dementia with Lewy bodies; treatment; cholinesterase inhibitor

Dementia with Lewy bodies (DLB) accounts for 15–20% of cases of dementia in old age (Perry *et al*., 1989) and presents clinically with fluctuating cognitive impairments, visual hallucinations and parkinsonism (McKeith *et al*., 1996). Psychotic symptoms are typically intrusive, persistent, distressing to both patient and carers and commonly lead to behavioural disturbances, including aggression. A diagnosis of DLB has important clinical consequences (Scully *et al*., 1998). It particularly serves as a warning against the use of neuroleptic medications, since patients with this disorder are very susceptible to severe extrapyramidal side effects which are probably mediated via dopamine D2 receptor blockade (Piggott *et al*., 1994) within an already severely compromised nigro-striatal dopaminergic system. These neuroleptic sensitivity reactions, which are sometimes reminiscent of the neuroleptic malignant syndrome, are associated with a 2–3-fold increase in mortality (McKeith *et al*., 1992). The newer atypical antipsychotics may be liable to induce similar adverse effects (McKeith *et al*., 1995; Walker *et al*., 1999).

Autopsy studies indicate that hallucinations in DLB are correlated with reduced neocortical cholinergic activity; cholinergic enhancement is therefore a more rational treatment alternative than dopaminergic blockade. In support of this hypothesis are anecdotal case reports that some patients who respond well to cholinesterase inhibitor therapy have Lewy bodies at autopsy (Levy *et al*., 1994; Wilcock and Scott, 1994), rather than Alzheimer's disease (AD) which was the clinically suspected diagnosis.

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Systematic clinical trials of cholinergic agents in DLB have not been conducted until now because of difficulties in correctly identifying patients antemortem. Consensus criteria for the clinical diagnosis of dementia with Lewy bodies were recently agreed (McKeith *et al*., 1996). Preliminary studies validating these clinical criteria against neuropathological findings (Mega *et al*., 1996; Perry *et al*., 1998) report a sensitivity for case detection of 0.75–0.83 and a specificity of 0.79–0.91, levels of diagnostic accuracy similar to those achieved for AD. Using these criteria, Shea *et al*. (1998) reported upon nine clinically diagnosed DLB patients who were treated with donepezil 5–10 mg (mean dose 7.8 mg daily). By both cognitive testing and family reports, cognition improved in seven and hallucinations were improved in eight. In three patients treatment resulted in worsening parkinsonism, although this responded to levodopa/carbidopa treatment in each case.

This report gives details of 11 patients treated with a cholinesterase inhibitor in an open-label study that assessed neuropsychiatric, cognitive and neurological function using standardised instruments.

METHODS

Using the Consensus clinical criteria for DLB (McKeith *et al*., 1996), a double-blind, placebo-controlled, multicentre study in the UK, Spain and Italy, has been in progress to test the efficacy and tolerability of the pseudo-irreversible cholinesterase inhibitor, rivastigmine (EXELON, Novartis). Patients of any age and either sex, with an MMSE score of 10 or more were eligible for treatment. Exclusion criteria were the presence of advanced, severe or progressive or unstable disease of any other type which could contribute to or complicate the assessment of the dementia, or severe gastrointestinal, liver or renal disease that could result in altered absorption, metabolism or excretion of rivastigmine. Because of the theoretical possibility of worsening extrapyramidal symptoms with a procholinergic treatment, patients with severe parkinsonism at baseline were excluded (defined either as a Hoehn and Yahr score of 3 or more, or a score of 3 or more on any one of the UPDRS subscale items for rigidity, tremor or bradykinesia). Neuroleptics, cognitive enhancers and any cholinergic or anticholinergic medications were excluded. The use of levodopa preparations was allowed so long as dose was maintained unchanged from baseline throughout the treatment period.

Following 20 weeks of blinded treatment, followed by a 3 week drug free period, participants were offered open label rivastigmine treatment, titrated fortnightly up to their individual maximum tolerated dose (maximum 6 mg bd.). Outcome measures recorded at week 23 (drug free) and repeated 12 weeks later (week 35) were,

- the Mini-Mental State Examination (MMSE) for cognitive performance (Folstein *et al*., 1975);
- the Neuropsychiatric Inventory (NPI) for psychosis and behavioural disturbance (Cummings *et al*., 1994). The NPI assesses severity and frequency of symptoms within 12 neurobehavioural domains by carer interview. Changes in individual symptoms are under-represented within the NPI total score, therefore data were also analysed for the four NPI subscale items (hallucinations, delusions, apathy and agitation) which best characterise the key neuropsychiatric syndrome of DLB;
- the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) for parkinsonism (Fahn and Elton, 1987).

Mean scores pre and post treatment were compared using paired *t*-tests for all scales.

RESULTS

Information is presented for the first 11 UK patients who completed 12 weeks of open label, rivastigmine treatment. There were eight men and three women, a male predominance which is slightly in excess of the usual 1.5:1 male:female ratio reported in most DLB samples. Mean age was 78.5 years (range 70–84). All were taking concomitant medications (mean number of other medications excluding topical and inhaled preparations = 3.3, mode = 3, range = 1–5). Two were taking levodopa preparations (cases 2 and 3), five chlormethiazole (cases 1, 4, 5, 9, 11), two temazepam (cases 6 and 8), one fluoxetine (case 9), and two H_2-receptor antagonists (cases 2 and 9). Case 10 was prescribed risperidone 1 mg twice daily because of continued behavioural disturbance during the double-blind phase and remained on this subsequently. All patients completed 12 weeks of open label treatment with a mean daily dose of 9.6 mg at endpoint. Six patients tolerated 12 mg

Table 1. Neuropsychiatric inventory (NPI) scores over the course of the trial

Patient age + gender	NPI subscale score (0–48) (hallucinations + delusions + apathy + agitation items)				NPI total score (0–144)				Exelon dose/day in open label (mg)
	Double-blind		Open label		Double blind		Open label		
	Week 0	Week 20	Week 23	Week 35	Week 0	Week 20	Week 23	Week 35	
78m	16	15	12	3	24	22	20	6	12
75m	11	16	20	4	13	24	30	10	9
70m	25	5	12	7	38	28	42	41	12
84m	9	0	19	6	12	2	36	10	12
81f	3	0	7	4	19	2	22	19	6
74f	5	9	10	3	23	22	23	6	12
81m	20	7	13	11	38	29	35	33	9
80m	3	0	0	1	5	3	0	2	12
80m	11	9	16	0	15	19	16	0	12
78m	18	30	27	22	34	55	52	61	6
82f	14	28	14	19	40	49	40	47	3
Mean (SD)	12.3 (7.1)	10.8 (10.6)	13.6 (7.1)	7.3 (7.2)	23.7 (12.2)	23.2 (17.5)	28.7 (14.4)	21.4 (20.8)	9.6 (3.2)
Change over 12-weeks open label		−6.4 (−46.7%) *$p = 0.011$				− 7.4 (−25.7%) *$p = 0.063$			

* Paired *t*-test.

Table 2. MMSE and UPDRS scores over the course of the trial

Patient age + gender	MMSE (30–0)				UPDRS (0–56)				Exelon dose/day in open label (mg)
	Double-blind		Open label		Double-blind		Open label		
	Week 0	Week 20	Week 23	Week 35	Week 0	Week 20	Week 23	Week 35	
78m	16	19	22	24	24	16	26	17	12
75m	17	19	14	26	16	30	37	30	9
70m	12	20	19	16	12	16	27	15	12
84m	21	18	21	18	30	30	35	37	12
81f	18	19	18	15	19	16	17	15	6
74f	24	27	28	29	6	11	9	9	12
81m	21	26	25	20	12	7	13	13	9
80m	19	24	18	22	14	12	13	9	12
80m	14	14	10	13	29	42	55	38	12
78m	18	17	16	17	4	9	10	3	6
82f	17	11	17	16	30	28	27	19	3
Mean (SD)	17.9 (3.4)	19.5 (4.8)	18.9 (5.0)	19.6 (5.1)	17.8 (9.4)	19.7 (11.1)	24.5 (14.1)	18.6 (11.5)	9.6 (3.2)
Change over 12-weeks open label		+ 0.7 (3.9%) *$p = 0.620$				−5.8 (−23.8%) *$p = 0.007$			

MMSE = Mini Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale. * Paired *t*-test.

daily, two reached 9 mg, two reached 6 mg, and one only 3 mg. No severe adverse side effects occurred, nausea and diarrhoea being the most common unwanted effects which restricted upward dose titration.

Tables 1 and 2 summarise results of changes in NPI, MMSE and UPDRS scores. Data are presented about the changes in score during the double-blind and open label phases. By week 35, the mean NPI total score was reduced by 26% compared with week 23 and the NPI subscale score had fallen by 47%. Reductions in mean scores for individual NPI items over this period were; delusions 73%, hallucinations 27%, agitation 45% and apathy 63%. Five of seven patients lost all of their delusions, three of eight patients

stopped hallucinating and three had significantly fewer or less troublesome hallucinations. Five of the 11 patients (45%) experienced clinically important improvements defined by a $>50\%$ reduction in NPI subscale score and in these patients mean NPI subscale scores for delusions, hallucinations, apathy and agitation fell by 77%.

Carers and patients regarded these improvements as substantial and carers consistently reported patients to be more alert and responsive. The Mini-Mental State Examination, which was designed as a screening tool for memory impairment, was not sensitive to these clinically observed attentional improvements, which were however reflected in a 63% fall in NPI apathy scores.

Unified Parkinson's Disease Rating Scale mean scores were significantly reduced by 5.8 points (24%; $p = 0.007$) between weeks 23 and 35.

DISCUSSION

Patients recruited for this small open label study were clinically diagnosed as having DLB using the Consensus criteria which have been shown to have high specificity > 0.9 (Perry *et al*., 1998; Holmes *et al*., 1999) assessed by neuropathological validation. The majority, if not all, of the clinical diagnoses were likely therefore to be correct. After 12 weeks of open label treatment with rivastigmine, mean NPI scores fell by 73% for delusions, 63% for apathy, 45% for agitation and 27% for hallucinations. These observations are broadly similar to those of Shea *et al*. (1998) and Kaufer *et al*. (1998) who reported clinically significant improvements in psychotic symptoms, behavioural disturbances and cognition, particularly delirium-like features, using donepezil in patients clinically diagnosed as DLB. Like these previous authors, we were struck by the extent of improvement in some of the patients who come from a group generally held to be very difficult to treat pharmacologically.

Open label treatment studies must always, however, be viewed with great caution and there are several possible interpretations of these clinical observations. Firstly, they may have been due to a combination of placebo and Hawthorn effects. One might expect such effects also to have been apparent during the earlier blinded phase, but inspection of Tables 1 and 2 shows that this was not generally the case. There were only modest reductions between weeks 0 and 20 in NPI total (-12%) and NPI subscale (-2%) scores and UPDRS scores worsened marginally ($+2\%$). These changes are small compared with those during the second phase when all patients received active treatment, suggesting that a true pharmacological effect was present. MMSE scores increased more during the blinded phase ($+15\%$) than during open label ($+4\%$), more consistent with an initial practice effect and not suggestive of a major Hawthorn effect during open label treatment.

A second possible interpretation of the data is that patients who were randomised to active medication during the blinded phase exhibited a withdrawal syndrome between weeks 20 and 23, developing symptoms which were subsequently responsive to reintroduction of rivastigmine. Inspection of Table 1 shows that although NPI total scores were similar at week 20 and baseline, by week 23 there was a 24% increase over week 20 scores ($p = 0.18$, n.s.). A 26% increase was also seen in the NPI subscale score ($p = 0.29$, n.s.). In those patients whose NPI total scores worsened during the drug withdrawal period (cases 3, 4 and 5), increased ratings of apathy, irritability/lability and agitation/aggression accounted for most of the deterioration, only one patient showing worsening of delusions and hallucinations back to baseline values. All three of these patients' NPI total scores fell during the 20 week blinded phase, suggesting that they may have been on active medication (details of treatment allocation had not been released at the time of preparing this report). If so, their deterioration during weeks 20–23, may represent the loss of an effective treatment response, rather than a drug withdrawal phenomenon.

UPDRS scores at week 23 were also increased over week 20 ($+24\%$) and this was statistically significant ($p = 0.01$). Worsening of motor symptoms would be a paradoxical phenomenon and the opposite of that which would be predicted for withdrawal of a procholinergic treatment, on the basis of the beneficial effects of muscarinic antagonists. The improvement in extrapyramidal motor symptoms observed during open label treatment is equally difficult to understand, but reflects an earlier report in which a 63% fall in mean motor UPDRS scores was seen in a demented Parkinson's disease (PD) population treated with tacrine. These patients had no prior exposure to cholinesterase inhibition (Hutchinson and Fazzini, 1996), and the findings could not be explained by reversal of prior drug withdrawal. By contrast Shea *et al*. (1998) reported worsening of

parkinsonism in 33% of their donepezil treated patients, during the treatment phase. These rather discrepant observations are indicative of the potential importance but complex interactions of non-muscarinic, nicotinic cholinergic receptor mechanisms in the control of basal ganglia function. More clinical experience of using cholinesterase inhibitors in patients with extrapyramidal disorders is likely to reveal considerable response heterogeneity, in both motor and neuropsychiatric symptoms.

A third possibility is that the observed effects represent a real pharmacological action of rivastigmine upon the core features of the disease. This would be consistent with theoretical predictions and previous case reports. If so, cholinesterase inhibition may offer a relatively safe and effective approach to a common and currently difficult therapeutic challenge and reduce the need for potentially hazardous neuroleptic prescriptions. The magnitude of effect on neuropsychiatric (non-cognitive) symptoms in DLB contrasts with the modest effects of several cholinesterase inhibitors upon cognition and global function in patients with AD (Rogers *et al*., 1998; Corey-Bloom *et al*., 1998; Cummings *et al*., 1998). Controlled trials, such as those already in progress, with further determine the extent to which cholinergic treatments are effective in DLB and whether such effects can be generalised to the management of neuropsychiatric symptoms in PD and AD (Cummings *et al*., 1993).

Current reservations concerning the limited effects of cholinesterase inhibitors in the management of dementia may be in part due to their use having largely been restricted to patients with pure AD and without significant neuropsychiatric symptoms, thereby excluding both treatment responsive target disease and symptoms.

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