Rivastigmine in subcortical vascular dementia: A randomized, controlled, open 12-month study in 208 patients

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Abstract

Subcortical vascular dementia (VaD) is characterized by executive dysfunction and behavioral problems, reflecting deterioration of the frontal lobe. This study aimed to determine whether rivastigmine, a dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), has any effects on the typical symptoms of subcortical VaD. Patients receiving rivastigmine showed a slight improvement in executive functions and in behavior. Side effects in both groups were tolerable and there were no study withdrawals. Moreover, there are no drug interactions with other therapies previously and concomitantly assumed. Improvements in domains that characterize subcortical VaD were observed, indicating that rivastigmine may have provided targeted treatment in areas of the brain that are particularly affected in this patient population.

Key words: cholinesterase inhibition, behavior, executive function, rivastigmine, vascular dementia

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Introduction

Vascular dementia (VaD) is associated with a large amount of heterogeneity, grouping together a broad category of patients in whom various manifestations of cognitive decline are attributed to cerebro- or cardiovascular disease. The National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) consensus criteria[1] help to define it. Furthermore, the NINDS-AIREN criteria list different pathologies that help to identify patients with different subtypes of VaD: multi-infarct dementia (multiple large and complete infarcts, hypoperfusion); strategic infarct VaD (strategic single infarcts); and subcortical VaD (small vessel disease, hypoperfusion). The International Classification of Diseases 10th revision (ICD-10) criteria only recently identified subcortical VaD as a major subtype.[2]

Subcortical VaD now incorporates the old entities "lacunar state" and "Binswanger disease" and relates to small vessel disease and hypoperfusion resulting in focal and diffuse ischemic white matter lesions and incomplete ischemic injury.[3,4] Two pathophysiological mechanisms

may lead to subcortical VaD.[5] The first involves the occlusion of an arterial lumen, and subsequently a complete lacunar infarct, and leads to dementia due to the disruption of neural pathways. The second mechanism involves critical stenosis and hypoperfusion of multiple arterioles, resulting in widespread areas of incomplete infarction of the deep white matter and consequent functional disruption of the neural network. The end stages of the two pathways are the old entities "lacunar state" and "Binswanger syndrome"; in practice, these usually converge.

In patients with subcortical VaD, ischemic lesions are particularly apparent in the prefrontal subcortical circuit, including the prefrontal cortex.[6] This deterioration of the frontal lobe is reflected in the fact that dysexecutive syndrome seems to be the core feature of subcortical VaD.[7,8] Memory impairment and attentional deficits are also apparent, and patients often experience mood changes such as depression, personality changes, and emotional lability. In particular, these behavioral symptoms can be a major cause of stress, anxiety, and concern for caregivers and frequently lead to the institutionalization of patients.

However, it has recently been found that, as with other types of dementia, the pathological changes observed in patients with VaD are associated with cholinergic deficits. Compared with normal rats, rat models of VaD have shown significantly reduced levels of the neurotransmitters acetylcholine (ACh) and choline in the cortex and hippocampus,[9,10] which appear to correlate with impaired learning and memory.[10,11] In human postmortem studies, choline acetyltransferase (ChAT) activity has been shown to be reduced in VaD patients, compared with controls.[12,13] In the human brain, ACh plays a pivotal role in the autoregulation of cerebral blood flow through the parasympathetic innervation of the circle of Willis and of the pial vessels,[14] and causes significant arterial relaxation by promoting the synthesis of vasodilator agents.[15] These studies in animals and humans clearly suggest that impairment of cholinergic function may contribute to the symptoms of VaD.

Three cholinesterase inhibitors are commonly prescribed: donepezil, rivastigmine, and galantamine. While donepezil and galantamine target only acetylcholinesterase (AChE), rivastigmine acts as a dual cholinesterase inhibitor, with selectivity for AChE and butyrylcholinesterase (BuChE).[16] Studies have indicated that both AChE and BuChE may co-regulate levels of ACh and could play important roles in patients with cholinergic deficits.[17] Due to the proven efficacy of rivastigmine in Alzheimer's disease (AD), the pharmacological rationale to provide cholinergic therapy for patients with VaD, and the preclinical evidence of the effects of epistigmine (a rivastigmine analogue that also inhibits both AChE and BuChE), we decided to study rivastigmine in a well-defined group of patients with subcortical VaD.

Methods

Patients

Study subjects were men and women aged 65 to 80 with Mini-Mental State Examination (MMSE) scores of at least 14 and satisfying the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for dementia. Study subjects also satisfied the criteria for probable VaD in accordance with the NINDS-AIREN criteria.[1]

A patient was diagnosed as having subcortical VaD when the CT scan showed moderate to severe ischemic white matter changes[18] and at least one lacunar infarct. Patients were not included in the study if they showed signs of nonlacunar territorial infarcts or radiological signs of normal pressure hydrocephalus. Brain CT scans were randomized and reassessed independently by two neurologists. In the case of disagreement, the scans were reassessed together with an experienced neuroradiologist who made the final decision. Patients with previous psychiatric illness or central nervous system disorders and alcoholism were excluded.

Study design

Study subjects were 208 men and women, not bedridden, aged 68 to 81, outpatients recruited from January 1, 2000, to December 31, 2002, who underwent a standardized baseline assessment that included a detailed history, physical examination, laboratory tests, and psychiatric evaluations. The physical examination included evaluations of pulse rate and rhythm, blood pressure, heart size and sounds, peripheral pulses, retinal vessel and carotid artery evaluation, and chest x-ray. Laboratory tests included assessments of urea nitrogen, creatinine, hemoglobin, glucose, glycosilated hemoglobin, thyroid stimulating hormone (TSH), thyroid hormones, vitamin B12 and folate levels, LDL and HDL cholesterol, triglycerides, urinalysis, and electrocardiogram (ECG).

Patients were divided into two homogenous groups, matched for age and education levels. Group A received rivastigmine 3-6 mg/day, while Group B received cardioaspirin 100 mg/day. Patients receiving rivastigmine began treatment on the lower dose of 3 mg/day and were titrated to the higher dose of 6 mg/day after 12 weeks. Patients in both groups were allowed to continue any previous therapy (e.g., antihypertensive, antidyslipidemic, antidiabetic drugs) (Table 1). Overall, the two treatment

Table 1. Types of comedications at baseline: Number of patients and mean doses of individual agents used		
Type of medication	**Group A: Rivastigmine 3 – 6 mg/day**	**Group B: Aspirin 100 mg/day**
ACE inhibitors	56 patients	54 patients
enalapril, mean (± SD) dose	26.3 ± 5.1 mg/day	24.98 ± 4.32 mg/day
ramipril, mean (± SD) dose	3.02 ± 3.1 mg/day	2.7 ± 2.92 mg/day
Sartan	14 patients	18 patients
losartan, mean (± SD) dose	50 ± 19.23 mg/day	60 ± 12.56 mg/day
telmisartan, mean (± SD) dose	35 ± 16.70 mg/day	32 ± 19.50 mg/day
Calcium antagonists	13 patients	11 patients
amlodipine, mean (± SD) dose	6.0 ± 4.10 mg/day	5.6 ± 2.34 mg/day
phelodipine, mean (± SD) dose	7.5 ± 2.21 mg/day	6.9 ± 3.5 mg/day
Nitroglycerine or analogue	21 patients	16 patients
isosorbide mononitrate, mean (± SD) dose	35.5 ± 10 mg/day	40.5 ± 10.6 mg/day
Antidiabetic medication	25 patients	23 patients
glimepiride, mean (± SD) dose	2.0 mg bid	2.0 mg bid
glibenclamine, mean (± SD) dose	5.0 mg bid	5.0 mg bid
Diuretics	15 patients	23 patients
amiloride or hydroclorothiazide, mean (± SD) dose	14.7 ± 7.50 mg/day	17.7 ± 3.50 mg/day
Bronchodilators	9 patients	7 patients
A combination of the above therapies	46 patients	43 patients

groups were well-matched, and no significant between-group differences were observed. However, previous or concomitant anticholinergic therapy was not permitted.

All patients completed the study and were followed for 12 months, with periodic neurological and neuropsychological examinations. Visits were scheduled to take place one, three, nine, and 12 months after the start of the treatment. A complete neuropsychological examination was conducted at baseline and at the last visit, and the results were compared.

The trial was conducted in accordance with the Declaration of Helsinki and with the Ethics Guidelines of the Institute. Written informed consent was obtained from all participants or their responsible caregivers prior to the study. Treatment compliance was monitored by the caregivers, who controlled the intake of drugs and reported any problems.

Outcome measures

Global performance was assessed using the Clinical Dementia Rating[19] at every visit. Global cognitive function was assessed using the MMSE[20] at each visit. In addition, since the MMSE is not sensitive to executive functions or mental slowing,[21] executive function was assessed using the Ten-Point Clock Drawing test (TPC)[22] at each visit. Word fluency was also assessed using phonological (WF phonol.) tests[23] at each visit.

Behavioral symptoms were assessed using the Behavioral Pathology in AD Rating Scale (BEHAVE-AD)[24] at every visit. In addition to the total BEHAVE-AD score, seven items from the scale were assessed individually: delirium (maximum score 21); hallucinations (maximum score 15); activity disorders (maximum

Table 2. Mean (± SD) and minimum-maximum outcome measure scores in the two treatment groups at baseline		
Measure	**Group A: Rivastigmine 3 – 6 mg/day**	**Group B: Aspirin 100 mg/day**
MMSE	19.75 ± 2.38 (15-24)	20.23 ± 2.45 (15-23)
Phonological fluency	17.87 ± 2.55 (13-23)	17.3 ± 2.18 (13-23)
TPC	5.2 ± 0.79 (4-7)	5.28 ± 0.72 (4-7)
BEHAVE-AD	39.75 ± 7.5 (23-53)	39.79 ± 7.02 (23-52)
GDS	13.46 ± 3.01 (4-18)	13.44 ± 2.31 (5-16)
CIRS	5.06 ± 0.93 (3-7)	4.75 ± 0.98 (3-7)

score 9); aggressiveness (maximum score 9); sleep disturbances (maximum score 3); affective disorders (maximum score 6); and anxiety and phobias (maximum score 12). The Geriatric Depression Scale (GDS)[25] was used at each visit to better define depression. Finally, global health condition was assessed using the Cumulative Illness Rating Scale (CIRS)[26] at every visit.

Tolerability

The incidence of side effects was recorded throughout the study. In particular, patients were monitored carefully for general complications; blood pressure was measured at each visit, and caregivers were instructed to monitor blood pressure and heart rates of the patients. Caregivers were instructed to report every complaint, such as gastric distress, muscle contractions, or other symptoms. In the case of specific symptoms being reported, it was our decision to complete the evaluation with a medical visit or to proceed with other laboratory or instrumental evaluation. The CIRS for comorbidities was assessed at each visit.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 10.0).

Table 3. Mean (± SD) changes in outcome measure scores compared with baseline, in the two treatment groups at 12 months		
Measure	**Change vs. baseline at month 12**	
	Group A: Rivastigmine	**Group B: Aspirin**
MMSE	-2.54 ± 1.08[a]	-3.97 ± 1.16[c]
Phonological fluency	-2.94 ± 1.24[b,c]	-2.88 ± 1.18[c]
TPC	-0.56 ± 0.77[a,b]	-2.71 ± 0.12[c]
BEHAVE-AD	-16.37 ± 7.5[c,d]	5.34 ± 7.08[c]
GDS	-3.91 ± 3.73[c,d]	1.00 ± 1.98[c]
CIRS	-0.12 ± 0.99	0.13 ± 0.98

[a] $p < 0.05$ versus baseline; [b] $p < 0.05$ versus the aspirin group; [c] $p < 0.01$ versus baseline; [d] $p < 0.01$ versus the aspirin group.

Table 4. Mean (± SD) changes in separate scores of BEHAVE-AD, compared with baseline, in the two treatment groups at 12 months		
BEHAVE-AD item	**Changes vs. baseline at month 12**	
	Group A: Rivastigmine	**Group B: Aspirin**
Delusions	0.06 ± 0.1	0.1 ± 0.23[a]
Hallucination	-2.86 ± 0.23[c,d]	0.89 ± 0.2[c]
Activity alterations	-1.28 ± 0.24[c,d]	1.1 ± 0.7[c]
Aggressiveness	-1.01 ± 0.9[c,d]	-3.25 ± 0.2[c]
Anxiety/phobia	-7.26 ± 1.9[c,d]	1.44 ± 1.2[c]
Sleep disturbances	-0.42 ± 0.2[c,d]	1.5 ± 0.2[c]
Affective disturbances	-0.54 ± 0.1[c,d]	0.45 ± 0.2[c]
Anxiety	-7.6 ± 1.23[c,d]	1.75[c]
Total BEHAVE-AD score	-16.37 ± 2.1[c,d]	1.44 ± 0.34[c]
[a] $p < 0.05$ versus baseline; [b] $p < 0.05$ versus the aspirin group (n/a); [c] $p < 0.01$ versus baseline; [d] $p < 0.01$ versus the aspirin group.		

Within-group changes from baseline to 12 months were tested using the Wilcoxon Signed Ranks test. Between-group comparisons of changes from baseline were tested using the Wilcoxon two-sample test. This was done for the overall scores for each efficacy variable. In addition, subanalyses of behavioral data obtained at baseline and at 12 months using the BEHAVE-AD were performed to determine which items of these scales showed particular improvements or deterioration. Results are presented as mean changes from baseline with standard deviations, and P-values are presented where appropriate.

Results

Patients

This study included 208 patients, 98 men and 110 women, with a diagnosis of probable subcortical VaD. Their mean age was 75.67 + 2.98 years, and they had a mean education level of 8.12 + 4.1 years. Abrupt onset was confirmed by all caregivers, and the mean duration of symptoms was estimated to be 6.56 + 7.12 months. Brain CT scans were available for all patients, and there was 94 percent inter-rater agreement for the two neurologists assessing the scans. All patients completed the full 12-month study. Of the 208 patients, 104 were randomized to receive rivastigmine (Group A) and 104 were randomized to receive cardioaspirin (Group B).The two groups were matched for comedications and concomitant illnesses (Table 1).

Efficacy of rivastigmine in patients with VaD

As Table 2 indicates, at baseline there were no statistical differences between the two groups on any of the scales, indicating the patients in each group were matched for baseline symptoms of dementia.

As shown in Table 3, patients in both treatment groups showed deteriorations in general cognition at 12 months compared with baseline, as assessed by the MMSE, but this was significantly worse in the aspirin group. Phonological fluency deteriorated in both groups over the course of the study. Executive function, as assessed using the TPC, showed a deterioration, too, but the between-group difference at 12 months was statistically significant ($p < 0.05$). There was a greater deterioration in group B than in group A when compared with baseline. On the BEHAVE-AD, total scores in the rivastigmine group were significantly improved over baseline and over the aspirin group at month 12 (all $p < 0.001$). Further analysis of the BEHAVE-AD individual items indicated that rivastigmine provided benefits on all items of the scale, except delusions, throughout the study (Table 4, Figures 1-3). Depression, as assessed using the

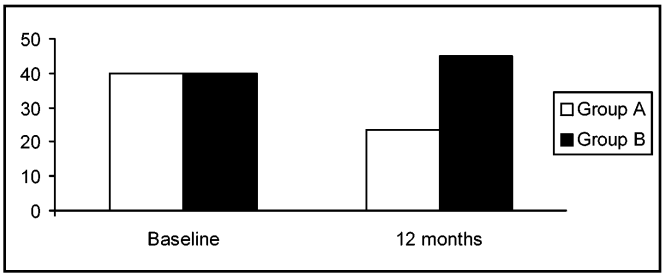

Figure 1. Changes in behavioral alterations, assessed using the BEHAVE-AD, in patients with subcortical VaD receiving rivastigmine (Group A) or cardioaspirin (Group B) for 12 months.

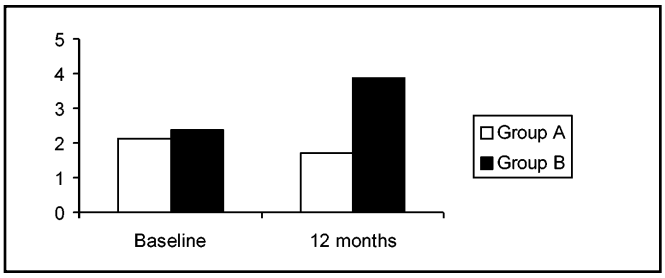

Figure 2. Changes in sleep alterations, assessed using the BEHAVE-AD, in patients with subcortical VaD receiving rivastigmine (Group A) or cardioaspirin (Group B) for 12 months.

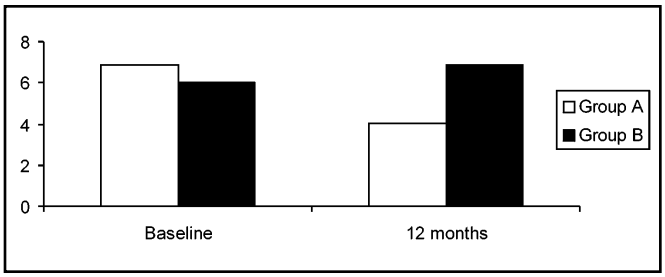

Figure 3. Changes in hallucinations, assessed using the BEHAVE-AD, in patients with subcortical VaD receiving rivastigmine (Group A) or cardioaspirin (Group B) for 12 months.

GDS, was significantly improved in the rivastigmine group ($p < 0.001$ versus baseline and versus the aspirin group). No effect could be detected in the comorbidities evaluation. Both drugs were well tolerated.

Tolerability of rivastigmine in patients with VaD

Of the patients in Group A, 21.15 percent reported transitory nausea during the titration phase; this resolved spontaneously within 4.4 ± 2.34 weeks. Muscle contractions were reported in 14.42 percent of patients during the titration phase, more often patients who assumed diuretics, but resolved spontaneously during the first week of reaching the target dose. Anorexia was exhibited by 12.5 percent of patients, especially when the therapy began during summer; 5 percent manifested episodes of postural hypotension during the titration phase, without cardiac involvement.

In Group B, 26.5 percent reported nausea during the first week of the study, associated with anorexia; and 25 percent reported heartburn throughout the study. Although patients were allowed to continue any previous medication, no side effects that were believed to be related to drug-drug interactions were reported.

Discussion

Successful trials in patients with VaD are limited. One post hoc subgroup analysis of the six-month Scandinavian Multi-Infarct Dementia Trial has shown that, although a treatment effect was not observed in the total trial population, the subgroup of subcortical VaD patients receiving nimodipine performed better on the majority of tests and functional scales, compared with patients given placebo.[4] Also, pentoxifylline[27] and propentofylline,[28] an adenosine uptake/phosphodiesterase inhibitor that has been suggested to have neuroprotective properties, have also shown promising results. Nevertheless, no drug can be positively recommended at present, and our data justify further, larger studies of cholinergic drugs for the treatment of vascular cognitive impairment. Most previous clinical trials performed in patients with VaD have achieved unsatisfactory results,[29] including a trial of the AChE-selective inhibitor galantamine.[30] In this study, galantamine showed efficacy in patients with AD with cerebrovascular disease (mixed dementia), but not VaD.[30-31] The drug's efficacy in mixed dementia may stem from its effects on the Alzheimer's aspect of the condition. In contrast, rivastigmine has now shown efficacy in both AD with vascular disease[32] and in subcortical VaD, indicating that its dual inhibitory treatment strategy may affect the cholinergic deficits underlying both conditions.

Our results are consistent with those of a previous, smaller study comparing rivastigmine 3-6 mg/day and aspirin 100 mg/day in 16 patients with subcortical VaD[33-36] and indicate that long-term treatment with rivastigmine resulted in a slight improvement in executive function and planning strategy (as demonstrated by TPC scores) and a general improvement in behavior and social conduct. This may be related to the well-known particular activity of rivastigmine in regions of the cortex associated with attentional processes and executive function.[37-39] Significant correlations have been observed

between AChE and BuChE inhibition and functions of frontal and temporal brain regions associated with attention for up to 12 months in patients with AD.[40-42] Since the frontal lobe in particular is known to be associated with executive and attentional functions, the brain region selectivity of rivastigmine may also explain its sustained efficacy in patients with subcortical VaD who show marked deficits in these domains, since the drug will have been acting upon particularly relevant areas of patients' brains. Furthermore, the brain region selectivity of rivastigmine may explain the beneficial effects on hallucinations observed in patients with subcortical VaD. Rivastigmine has also previously demonstrated benefits in hallucinations in patients with the Lewy body variant of AD[43,44] and those with Parkinson's disease dementia.[45] Hallucinations are particularly associated with temporal regions of the brain,[44] an area for which rivastigmine has shown a preferential affinity. To confirm a previous, though limited observation,[36] this study also reported an amelioration of sleep disturbances in patients taking rivastigmine. This statement has no anatomical or biochemical foundation, but it may in part reflect the described reductions in anxiety, agitation, and hallucinations in patients treated with rivastigmine.

Furthermore, long-term rivastigmine was well tolerated. Cholinergic effects were reported during the escalation phase, but none of these led to study withdrawal, and no treatment-related effects emerged during maintenance treatment. This is probably due to the brain-selectivity of rivastigmine,[16] which minimizes effects of the drug on peripheral enzymes, and its brain region selectivity,[37-42] which minimizes effects on non-targeted areas of the brain. Rivastigmine appears to have a very low potential to induce adverse cardiac or respiratory effects.[46] No drug-drug interactions were reported in the current study. Rivastigmine is metabolized by its target enzymes, AChE and BuChE,[46,47] and this—along with its short half-life in the peripheral circulation, low plasma protein binding, and brain selectivity—suggests that rivastigmine is unlikely to interact with other medications,[47] offering an important advantage in elderly patients who typically take many different medications for concurrent illnesses. This is particularly important in patients like those selected for our study, with vascular risk factors, since they are likely to be receiving a number of other concomitant medications.

The results from this follow-up study suggest that rivastigmine is useful in subcortical VaD; however, the conclusions in this and other open-label studies need to be addressed in controlled clinical trials.

Our suggestion is that VaD is not a univocal and unique pathology; the etiopathogenesis of multi-infarct dementia and that of subcortical vascular dementia are quite different. Future studies need to consider those entities separately to obtain good results.

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