Clinical Neuropharmacology
Vol. 26, No. 6, pp. 317–321

Effects of Rivastigmine on Cognitive Function and Quality of Life in Patients With Schizophrenia

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Summary: We aimed to determine whether the cholinesterase inhibitor rivastigmine, an inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), would improve quality of life and cognitive function in 16 clinically stable subjects affected by schizophrenia in the residual phase. Study subjects began rivastigmine treatment at a dose of 1.5 mg bid. This dose was escalated at monthly intervals in increments of 1.5 mg bid to a maximum of 6 mg bid. All subjects were followed for 12 months. Quality of life was assessed using the Satisfaction with Life Domains Scale (SLDS, a self-report scale containing 10 "satisfaction" items); cognitive function, attentional function, and aspects of learning and memory were evaluated using common neuropsychological tests. Psychopathology was evaluated by means of the Brief Psychiatric Rating Scale (BPRS). Rivastigmine treatment resulted in significant improvements in quality of life, which were paralleled by significant improvements in cognitive function, learning and memory, and trends for improvement in attention. The BPRS factor "anergia" showed significant improvement, while low baseline scores in other psychotic factors did not permit further improvements. There were no reports of nausea or vomiting. In conclusion, rivastigmine significantly improved quality of life in subjects with schizophrenia. These benefits may relate to the drug's effects on cognitive deficits and negative symptoms associated with the condition. **Key Words:** attention, cholinesterase inhibition, psychosis, quality of life, rivastigmine, schizophrenia

INTRODUCTION

Schizophrenia is a psychotic disorder that is characterized by profound changes in personality, behavior, and perception. In addition, patients with schizophrenia often experience attentional deficits, memory problems, and executive dysfunction. The inability to cope with these deficits and associated distress substantially contributes to reduced quality of life in patients with schizophrenia.[1]

Although dopamine has conventionally been regarded as the key neurotransmitter involved in the pathogenesis of schizophrenic symptoms,[2] there are a number of studies implicating a role of cholinergic neurons in the disease. The obvious pathology of the cholinergic system as seen in Alzheimer's disease (eg, decreased cell density in the nucleus basalis of Meynert) is absent from the brains of schizophrenic patients, but decreases in brain choline acetyltransferase (ChAT) levels at postmortem have been shown to be significantly correlated with the severity of antemortem cognitive impairments.[3] The cholinergic deficits associated with schizophrenia provide a rationale for the evaluation of cholinesterase inhibitors in schizophrenic patients.

A recent double-blind study of the acetylcholinesterase (AChE)-selective inhibitor donepezil failed to demonstrate benefits in patients with schizophrenia,[4] although 2 earlier case studies indicated that this drug may improve neuropsychological functioning in these patients.[5,6] Beneficial effects on negative symptoms of schizophrenia were reported in a single patient receiving another AChE-selective inhibitor, galantamine, for 2 months,[7] and physostigmine has been reported to have beneficial effects on visuospatial working memory in patients with schizotypal personality disor-

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der.[8] A case study with the butyrylcholinesterase (BuChE)-selective inhibitor ethopropazine also demonstrated significant improvements in cognitive function in a schizophrenic patient.[9] These studies did not evaluate the effects of treatment on quality of life.

Since both AChE and BuChE are involved in the regulation of ACh in the human brain,[10] agents that inhibit both AChE and BuChE, such as rivastigmine, may provide additional benefits in demented patients.[11–13] Therefore, we aimed to determine whether the inhibition of both cholinesterases with rivastigmine would improve quality of life and contributing symptoms in a group of schizophrenic patients, when it was added to their current antipsychotic treatment regimens.

METHODOLOGY

Study Subjects

Subjects eligible for study inclusion were men and women aged 18 to 50 years and satisfying the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria[14] for schizophrenia in the residual phase. Subjects had to have been diagnosed with schizophrenia at least 2 years before study entry, and the condition had to be considered clinically stable by the investigator. Before entering the study, subjects needed to be willing and able to provide informed consent. In the residual phase of schizophrenia there is still some disturbance, but florid symptoms have abated, and a high level of psychotic symptoms was therefore an exclusion criterion. Subjects with a history of substance abuse or somatic disease during the previous year, acute psychotic episodes during the past 2 years, or somatic illnesses were excluded from the study.

Study Design

This was a single-center (Psychiatric Rehabilitation Unit, University of Pisa, Italy), open, 12-month study of rivastigmine in subjects with schizophrenia. After written informed consent was obtained, the diagnoses were confirmed by means of a Structured Clinical Interview for DSM (SCID) for schizophrenia, and physical examinations were performed to assess the health of the subjects. Subjects began rivastigmine treatment at a dose of 1.5 mg bid. This dose was escalated at monthly intervals in increments of 1.5 mg bid to a maximum of 6 mg bid. Subjects were allowed to continue any previous medications except anticholinergic therapies. All subjects were followed for 12 months, with periodic neuropsychological examinations. Visits were scheduled to take place 1, 2, 3, 4, and 12 months after the start of treatment. The study was conducted in accordance with the Declaration of Helsinki and with the Ethics Guidelines of the Institute.

Outcome Measures

Several outcome measures were used to evaluate the efficacy of rivastigmine treatment in subjects with schizophrenia. Quality of life was assessed with the Satisfaction with Life Domains Scale (SLDS),[15] a self-report scale containing 10 "satisfaction" items. The Mini Mental State Examination (MMSE)[16] was used to assess overall cognitive performance. The Continuous Performance Test (CPT)[17] evaluated sustained attentional function, and the Wechsler Memory Scale (WMS)[18] evaluated aspects of learning and memory. Tolerability assessment was based on spontaneous reports of adverse events by subjects. The Brief Psychiatric Rating Scale (BPRS)[19] was used to detect the emergence or worsening of psychiatric symptoms.

Statistical Analyses

Statistical analyses were based on subjects completing the 12-month study. Changes in scores were compared with those at baseline using the two-tailed paired Student *t* test. A P value of ≤ 0.05 was considered statistically significant.

RESULTS

Study Subjects

Sixteen subjects were included in the study. They had a mean (± SD) age of 32 (± 8) years, and 60% of subjects were men. Most (87.5%) were unmarried or divorced. All subjects were taking concomitant atypical antipsychotics: 9 were taking clozapine (mean dosage 200 mg/d; range 50–500 mg); 5 were taking risperidone (4 on 6 mg/d and 1 on 4 mg/d); and 2 were taking olanzapine (both 20 mg/d).

The mean baseline MMSE score was 26.4 (± 3.1), reflecting only very mild global cognitive impairment (the best possible score on the MMSE is 30). Mean baseline scores on the SLDS, WMS, and CPT were 74.4 (± 15.6), 47.4 (± 12.6), and 9.0 (number of misses) (± 8.3), respectively. At the end of the study, final doses of rivastigmine were lower than expected. Only 1 patient received 12 mg daily; 3 received 6 mg daily and 6 received 3 mg daily.

Ten subjects completed 12-months of rivastigmine treatment. Reasons for early discontinuation in the other 6 subjects were withdrawn consent (2 subjects, during the first and second month of treatment), low

treatment compliance (1, after the first evaluation), and the emergence of psychomotor agitation (three, 1 at the beginning of treatment and 2 during the third month).

Efficacy of Rivastigmine

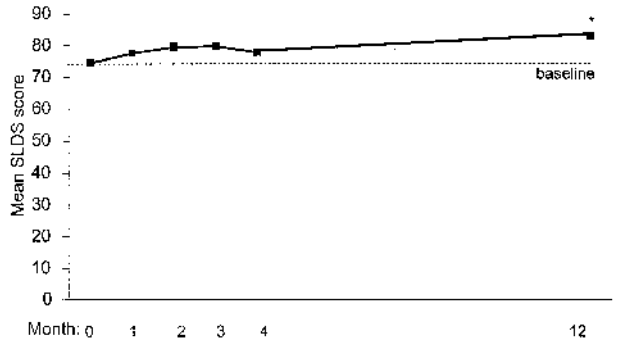
Rivastigmine treatment resulted in statistically significant improvements in quality of life, as assessed using the SLDS (Figure 1). Total SLDS scores were improved from 74.4 points at baseline to 82.9 points at 12 months ($P = 0.03$). In particular, improvements were seen in individual SLDS items relating to mood ($P = 0.016$) and social relationships ($P = 0.047$) at month 12.

At baseline, mean MMSE scores (26.4 points) demonstrated very mild cognitive impairment; only 3 subjects entering the study had baseline scores of less than 26 on the MMSE. Nevertheless, MMSE scores were improved over baseline at each post-baseline visit, and these improvements reached statistical significant at months 1, 3, 4, and 12 (Figure 2). Mean WMS scores indicated that learning and memory performances were improved over baseline at all post-baseline visits, with statistical significance being reached at all time-points (Figure 3). Results on the CPT indicated that sustained attentional function was initially improved in schizophrenic patients receiving rivastigmine. Statistically significant reductions in the number of "misses" were reported at month 2 ($P = 0.004$) and month 3 ($P = 0.045$), although at month 12, CPT scores were not statistically significantly different from baseline.

Tolerability of Rivastigmine

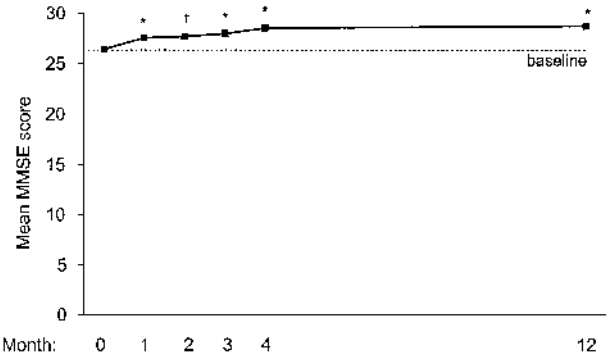
No subjects showed physical adverse events during the study, and there were no reports of nausea or vomiting. Three subjects withdrew because of psychomotor agitation. It was thought possible that these events were due to rivastigmine treatment because they occurred during the first months of treatment and disappeared after treatment interruption.

There was no change in BPRS factor scores showing psychotic symptoms, indicating that rivastigmine did not cause treatment-emergent psychotic symptoms. Analysis of BPRS factors also showed a significant ($P < 0.05$) decrease from baseline in the factor "anergia" (the factor most similar to negative symptoms) after 1 month, and this improvement persisted at all following evaluations except month 4.



*$p < 0.05$ *versus* baseline

FIGURE 1. Changes in mean total quality of life (SLDS) scores over the study (n = 10).

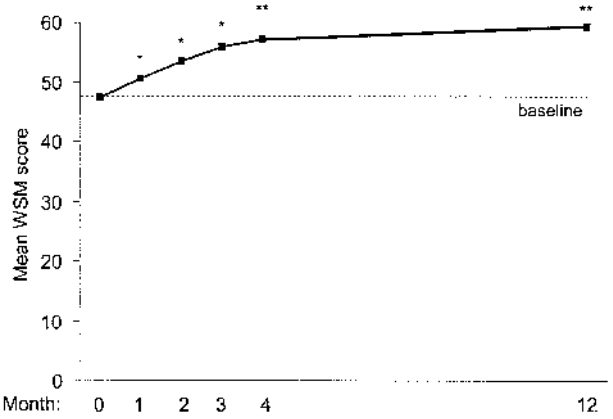


* $p < 0.05$
† $p = 0.06$

FIGURE 2. Changes in mean MMSE scores over the study (n = 10).

DISCUSSION

To our knowledge, this is the first study demonstrating beneficial effects of any cholinesterase inhibitor on cognitive deficits, negative symptoms and quality of life of patients affected by schizophrenia. Significant improvements appeared after only one month of treatment and were particularly notable because baseline as-



* $p < 0.01$ *versus* baseline
** $p \leq 0.001$ *versus* baseline

FIGURE 3. Changes in mean WMS scores over the study (n = 10).

sessments indicated that the study subjects were not markedly cognitively impaired. The early response suggests that it is unlikely that the improvements were spontaneous, even considering a potential placebo response. However, the open study design cannot conclusively distinguish between spontaneous recovery and the effects of rivastigmine.

Hussain et al[20] also recently reported improvements in attention, memory, and problem-solving with improved social and vocational functioning in 7 schizophrenic patients receiving rivastigmine. Benefits on attention are particularly important, not only because they are a key feature of dementia in schizophrenia, but also because attentional functions probably underlie a range of other symptom domains, such as memory, apathy, and the ability to perform normal daily activities. In contrast, the failure of donepezil to provide benefits in a recent study involving patients with schizophrenia[4] may reflect the fact that donepezil is reported to have weak effects on attention.[21–23] The benefits of rivastigmine in this population may also reflect the inhibition of BuChE (as well as AChE).

Although all cholinesterase inhibitors are usually associated with nausea and vomiting, these events were not reported in the current study. A relative absence of centrally mediated cholinergic side effects such as nausea and vomiting may be expected in patients with schizophrenia, due to the blockade of dopamine receptors in the area postrema by chronic antipsychotic therapy. For example, in previous studies, patients receiving dopaminergic or antipsychotic medication prior to treatment with cholinesterase inhibitors reported lower incidences of these side effects than might have been expected.[24–26] The low number of patients with nausea and vomiting may also reflect the relatively low doses, and the slow escalation, of rivastigmine. The incidence of side effects may also have been under-reported since we relied on spontaneous reporting rather than clinician directed investigations, although it was thought sufficient to rely on spontaneous reporting in residual phase patients.

The three withdrawals due to the emergence of psychomotor agitation were unexpected, since rivastigmine has not been previously associated with motor symptoms, even in patients at a high risk of these events such as those with Lewy body dementia or Parkinson's disease.[24,27] All 3 withdrawals occurred during the first 3 months of treatment, and seemed to be linked to intolerance of, or increased doses, of rivastigmine. The typical incidence of psychotic decompensation in untreated schizophrenic patients appears to be in the region of 29% per year[28] or 82% over 5 years.[29] Rivastigmine was not associated with the emergence of psychotic symptoms in this study.

The results of the current study should be interpreted with caution, because it was an open study with no control group, and it involved only a small number of subjects. The analysis was based only on the 10 subjects completing the study, to gauge the effects of long-term treatment in this population. This selection may have biased the results. Nevertheless, considering the exploratory aims of this study, an analysis on completers may be considered acceptable. The results are encouraging, and warrant further investigations into the use of rivastigmine in schizophrenia.

In conclusion, dual inhibition of AChE and BuChE with rivastigmine resulted in significant improvements in a group of schizophrenic subjects with negative symptoms. The improvements in quality of life were clinically relevant, and are likely to have important benefits in this population. Further studies in schizophrenic patients with greater baseline impairments will be interesting, especially in terms of the pharmacological mechanisms underlying the drug effects.

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