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Schizophrenia Research 59 (2002) 29–33

SCHIZOPHRENIA RESEARCH

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An open-labeled trial of adjunctive donepezil for cognitive impairments in patients with schizophrenia

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Received 26 July 2001; accepted 5 November 2001

Abstract

A pilot study was conducted to examine if donepezil could enhance cognitive function in patients with schizophrenia. Fifteen subjects who were on stable olanzapine treatment were entered into a 6-week open-labeled trial of donepezil. Subjects received baseline and end-of-study P50 and neuropsychological assessments. Donepezil treatment resulted in significant improvement in manual dexterity. There were moderate improvements in verbal recall memory and visual memory and processing speed, with smaller changes in P50 and verbal recognition memory. There was no effect on an attention measure. There were no changes in either positive or negative symptoms. These results suggest that cholinergic tone modulation may enhance selective behavioral functions in patients with schizophrenia, but further study is required to delineate the full extent of the potential benefit of this approach.

Keywords: Donepezil; Cognitive impairments; Schizophrenia

1. Introduction

Patients with schizophrenia are characterized by a broad range of cognitive impairments (Goldberg and Gold, 1995). These include impairments in attention; visual and verbal memory; working memory; processing speed; abnormalities in sensory gating, as measured by P50; and eye-tracking. Cognitive impairments are hypothesized to be a major determinant of the poor social and occupational functioning observed in schizophrenia (Green, 1996). Conventional antipsychotics have limited beneficial or deleterious effects on cognition in patients with schizophrenia (Blyler and Gold, 2000). New generation antipsychotics may have modest benefits for cognitive function (Keefe et al., 1999), but whether these benefits represent a direct cognitive enhancing effect or an indirect effect through decreased adverse side effects has not been established (Blyler and Gold, 2000). Regardless, patients with schizophrenia continue to exhibit pronounced cognitive impairments despite adequate new generation antipsychotic treatment (Purdon et al., 2000).

Adjunctive pharmacotherapy may offer a viable alternative approach for the treatment of cognitive impairments. Adjunctive agents can be used to mod-

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PII: S0920-9964(01)00387-5

ulate specific neurotransmitter systems that are hypothesized to be involved in the pharmacology of specific cognitive functions.

Acetylcholine acts at muscarinic and nicotinic cholinergic receptors. These receptors are broadly distributed through the brain, including the neocortex, hippocampus, and basal ganglia (Cummings, 2000). Cholinergic mechanisms have been implicated in the regulation of attention, memory, processing speed, and sensory gating processes (Vitiello et al., 1997; Broocks et al., 1998; Furey et al., 2000); processes which are impaired in patients with schizophrenia. Further, acute nicotine administration has previously been shown to improve sensory gating, as measured by P50, in patients with schizophrenia (Adler et al., 1998).

Donepezil is a selective acetylcholinesterase inhibitor that has been demonstrated to produce improvement on general measures of cognitive impairment in patients with Alzheimer's disease (Rogers et al., 1998). However, its efficacy for specific cognitive functions has not been evaluated. In the current study, we examined the feasibility of using adjunctive donepezil for the treatment of cognitive abnormalities in patients with schizophrenia.

2. Methods

Fifteen patients were selected for entry into a 6-week, open-labeled study. Patients were diagnosed using a best estimate diagnostic approach and met DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder. All patients had been treated with olanzapine for a minimum of 6 months. Patients with concurrent substance abuse; organic brain disorder; mental retardation; or medical conditions that could be exacerbated by donepezil were excluded from the study. All patients provided written informed consent prior to the study entry.

Patients were administered a five-item neuropsychological test battery and the P50 paradigm at baseline and 6 weeks. The battery is presented in Table 1. Alternate forms of the Benton Visual Retention (BVRT) and Rey Auditory Verbal Learning (RAVLT) tests were used for the two test occasions. P50 was

Table 1
Donepezil study: baseline and end-of-study P50 and neuropsychological test measures (mean±S.D.)

	Baseline	Week 6	Effect size	*t*(*df*)	*p*
P50					
Click 2/click 1 amplitude ratio	0.74±0.46	0.57±0.26	0.30	−1.11 (13)	0.14
Verbal memory					
Rey Auditory Verbal Learning Test					
Trials 1–5 total score	33.8±11.9	36.4±10.0	0.46	1.73 (13)	0.11
Hits-False Alarms	8.5±5.9	9.3±6.5	0.31	1.13 (12)	0.28
Visual memory					
Benton Visual Retention Test					
Number correct	4.6±4.1	3.8±2.2	−0.24	−0.89 (13)	0.39
Error score	14.6±9.1	11.2±5.9	0.57	−2.14 (13)	0.05
Manual dexterity					
Grooved Pegboard					
Mean Dominant Hand+Non-Dominant Hand *t*-score	25.8±13.4	30.8±12.0	0.93	3.47 (13)	0.004
Processing speed					
WAIS-III Digit Symbol					
Scaled score	5.4±1.7	6.0±1.7	0.48	1.80 (13)	0.10
Attention					
GDS continuous performance test					
Hits-False Alarms	29.9±11.0	25.3±23.8	−0.17	−0.58 (10)	0.58

recorded from the vertex electrode referenced to linked ears during a paired-click paradigm, while subjects were seated with their eyes open. Artifact-free trials (voltage less than 50 μV) were averaged separately for clicks 1 and 2 to provide measures of P50 amplitude, latency, and sensory gating (i.e., click 2 Amplitude/click 1 Amplitude) (Freedman et al., 1996). The Brief Psychiatric Rating Scale (BPRS) positive symptom items (i.e., conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content) and the Scale for the Assessment of Negative Symptoms (SANS) total score (minus the inappropriate affect, poverty of content of speech, attention subscale, and global items) were used to assess positive and negative symptom change, respectively. The BPRS and SANS were administered at baseline and 6 weeks.

Patients were started on donepezil 5 mg/day, and the dose was increased to 10 mg/day after 4 weeks of treatment. Patients were on stable doses of olanzapine and any concurrent medication throughout the duration of the study.

T-tests and effect size (ES) estimates [$(\text{mean}_{\text{week 6}} - \text{mean}_{\text{baseline}})/\text{SD}_{\text{change score}}$] were used to assess baseline and week 6 differences in P50 and neuropsychological test scores (Cohen, 1987). *T*-tests were also used to examine change in symptom ratings.

3. Results

Fifteen patients entered and 14 patients completed the study. One patient withdrew with a complaint of sedation. The demographic characteristics of the patients who completed the study were: mean (±S.D.) (age: 43.1±6.6; 71% male; 78% Caucasian; and mean (±S.D.) duration of illness: 24.7±7.2. The mean (±S.D.) olanzapine dose was 25.7±11.9 mg/day. Two patients were receiving benzodiazepines, two patients were receiving antidepressants, and one patient was receiving valproic acid.

Patients demonstrated clear baseline cognitive impairments on the P50 and neuropsychological measures, with mean test scores 1–2 standard deviations below normative values (see Table 1). Donepezil treatment was associated with only a modest improvement in P50 suppression, i.e., a reduction in the click 2/click 1 ratio (ES=0.30). P50 suppression was normalized in five of the nine patients who had abnormal P50 sensory gating at baseline. The improvement in P50 was primarily due to a reduction in the amplitude of the response to click 2 (baseline: 2.15±1.66; end-of-study: 1.83±1.72). There was a very small change in the amplitude of the response to click 1 (baseline: 3.17±1.72; end-of-study: 3.05±2.08). There were no changes in P50 latency for either click 1 or 2.

Donepezil had a variable effect on neuropsychological test performance, with the largest effect size observed for the Grooved Pegboard measure, where improvement reached conventional level of significance. There were moderate improvements in the BVRT visual memory (Error score; ES=0.57) and RAVLT verbal recall memory (Trials 1–5 total score; ES=0.46) measures and the Digit Symbol processing speed (ES=0.48) measures, whereas there was only a small effect on the RAVLT recognition memory measure (Hits-False Alarms; ES=0.31). The BVRT (number correct) and Gordon Diagnostic System (GDS) continuous performance test (with distractors) measures did not improve with treatment.

There were no significant changes in either the BPRS positive symptom item total score (mean (±S.D.), baseline: 9.3±3.8; week 6: 8.2±3.8; $t=-1.55$, $df=14$, $p=0.14$) or the modified SANS total score (mean (±S.D.), baseline: 29.7±10.9; week 6: 30.0±12.6; $t=0.15$, $df=14$, $p=0.88$).

4. Conclusions

The study results suggest that adjunctive donepezil treatment may be associated with enhanced performance on selected behaviors and cognitive functions in patients with schizophrenia. Donepezil was well tolerated; only one patient dropped out of the study and nine of the remaining subjects chose to continue on the drug beyond the protocol.

The most pronounced effect was observed for the Grooved Pegboard manual dexterity measure. This is an unanticipated, but potentially important result. Patients with schizophrenia are characterized by slow motor movements, with such observations predating the advent of antipsychotic treatment (Kraepelin, 1919; Huston et al., 1937). The enhancement of motor speed may have a general benefit across a broad range of behaviors and cognitive functions. The mechanism

underlying motor speed enhancement is unknown and the result is potentially counterintuitive in light of the use of anticholinergic agents to treat parkinsonian symptoms, including akinesia, in patients with schizophrenia. However, a similar result was observed in a study examining the efficacy of the acetylcholinesterase inhibitor, rivastigmine, in patients with Lewy-body dementia (McKeith et al., 2000). Rivastigmine treatment was associated with significant improvement in motor symptoms and enhanced motor and processing speed. McKeith et al. (2000) suggested that these observed benefits may reflect the role of nicotinic receptors in the regulation of basal ganglia function. Alternatively, nicotinic receptors are known to regulate monoaminergic neurotransmitter release and acetylcholinesterase inhibitors may exert their beneficial effect on motor speed through these mechanisms (Li et al., 1998).

Moderate effect size improvements were observed on verbal recall memory, processing speed, and visual memory. On the visual memory test, patients exhibited a substantial decrease in BVRT error score, but had a small worsening in BVRT number correct (less than one item). The discrepancy between the two BVRT measures may reflect differences in the observed score distributions, which result from the nature of the scoring criteria for these measures. BVRT number correct is a yes/no categorization, whereas there are several ways to make BVRT figure errors, particularly in the context of a low number of correct items, as is observed here. The subsequent increased variability of the error score may lead to increased sensitivity of this measure to change (Hoff et al., 1996).

Patients treated with donepezil exhibited a greater than 20% decrease in the P50 amplitude ratio to repeated auditory stimuli. The improvement in P50 was primarily due to a reduction in the amplitude of the response to click 2, which suggests that donepezil may have a modest beneficial effect on the sensory gating process per se. There was no effect of donepezil on the GDS continuous performance test.

An important aspect of the study was that improved neuropsychological test performance occurred in the context of concurrent olanzapine treatment. Olanzapine has been shown to improve P50 (Light et al., 2000) and enhance neuropsychological test performance, including verbal and visual memory (Purdon et al., 2000). The observed benefit of adjunctive donepezil for verbal and visual memory may reflect a reversal of the adverse effect of olanzapine's muscarinic receptor antagonist activity. This inherent muscarinic receptor antagonist activity may offset some of the potential benefit of olanzapine for these memory measures, and may explain why donepezil was able to further enhance these functions in patients who would have already benefited from olanzapine treatment.

There was no significant change in either positive or negative symptoms. Cummings (2000) has argued that acetylcholinesterase inhibitors may have a beneficial effect on behavior that extends to the amelioration of positive psychotic symptoms. The lack of such an effect in the current study may be due to the clinically stable nature of the study subjects, insufficient power to detect such an effect, or this effect which has been reported in patients with dementia may not extend to the positive symptoms of schizophrenia.

The open-labeled design and lack of a control group raise the concern that the observed changes in P50 and neuropsychological test performance might represent practice, rather than drug, effects. However, this is unlikely to be an issue with P50, alternate forms were used for the RAVLT and BVRT, and the Grooved Pegboard and WAIS-III Digit Symbol tests are not especially prone to practice effects (Lezak, 1995). In addition, patients did not exhibit improvement across all measures. A second methodological issue is the trial duration. Patients only received the optimal donepezil dose (i.e., 10 mg/day) for the last 2 weeks of the trial. A longer exposure to this higher dose may have led to even more pronounced therapeutic effects.

In summary, these preliminary results suggest that adjunctive donepezil may have beneficial effects for selected behavioral and cognitive functions in patients with schizophrenia. The extent and eventual clinical utility of this pharmacological approach need to be evaluated with a double-blind study design that incorporates a more comprehensive cognitive battery.

Acknowledgements

The study was funded in part by Grants MH40279 and MH45074, and the UMB-Novartis collaboration.

We would also like to acknowledge Pfizer Pharmaceutical for their provision of the study medications, and Royce W. Waltrip, II, M.D. for his scientific contributions.

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