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Donepezil augmentation of clozapine monotherapy in schizophrenia patients: a double blind cross-over study

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Increasing evidence suggests that the cholinergic system is involved in the pathogenesis of schizophrenia. Donepezil, a central cholinesterase inhibitor, improves psychotic symptomatology in demented patients, however, evidence for its role in the management of active psychosis in schizophrenia remains limited. An 18-week double blind cross-over study was conducted in which eight patients were randomly assigned to either donepezil (5 mg/day for the first 4 weeks and 10 mg/day for the following 4 weeks) or placebo as augmentation treatment to clozapine. After this initial phase, there was a 2-week washout period of the study medication after which the same regimen was crossed over at the same dose and for the same period (8 weeks). No significant difference was noted in the total positive and negative symptom scale scores when donepezil was compared with placebo ($16.7\% + 12.97\%$ vs $3.20\% + 13.94\%$ respectively, $p = 0.18$). However, three patients improved (>15%) in the total PANSS scores (37.03%, 16.6% and 25.33%) during the donepezil treatment phase, while only one patient improved (20.87%) during the placebo phase. No differences were noted in the Calgary depression scale ($p = 0.305$), Simpson Angus scale ($p = 0.374$), clinical global impression-improvement scale ($p = 0.23$) and clinical global impression-severity of illness scores ($p = 0.116$). Although this preliminary study failed to demonstrate a clear effect of donepezil augmentation in clozapine treated chronic schizophrenia patients, it seems that the subtle positive effect of donepezil observed in some of our patients should encourage further investigation in a larger sample of this patient subpopulation. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — donepezil; clozapine; acetylcholine; cholinergic receptors; schizophrenia

INTRODUCTION

Recent studies suggest that the cholinergic system plays an important role in the pathogenesis of schizophrenia (Cummings, 2000; White and Cummings, 1996; Tandon 1999; Hyde and Crook, 2001; Raedler *et al.*, 2003; Dean *et al.*, 2002; Carlsson, 1988; Tandon *et al.*, 1991; Ichikawa *et al.*, 2002a; Felder *et al.*, 2001; Borda *et al.*, 2002). Donepezil, a centrally active relatively specific acetylcholinesterase inhibitor, has been shown to be beneficial in the management of symptoms of memory and cognitive dysfunction in patients with mild to moderately severe Alzheimer disease (Rogers *et al.*, 2000). The rationale for the use of a cholinesterase inhibitor such as donepezil in schizophrenia is based on the assumption that reduced cholinergic activity may contribute to cognitive impairment in schizophrenia. This may in turn be alleviated by increasing cholinergic activity at muscarinic and nicotinic receptors (Karson *et al.*, 1996; Crook *et al.*, 2000; Freedman *et al.*, 1995; Leonard *et al.*, 1996). To date there are four reports on the beneficial effect of donepezil on cognitive dysfunction in schizophrenia (Risch *et al.*, 2001; Buchanan *et al.*, 2002; Friedman *et al.*, 2002; Howard *et al.*, 2002) and two reports (Stryjer *et al.*, 2002, 2003) of the beneficial effect of donepezil in schizophrenia with comorbid dementia. It is important to note that none of these reports have demonstrated any efficacy of donepezil on the management of psychotic symptoms in schizophrenia patients. Despite the apparent lack of evidence indicating any beneficial effect of donepezil

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in the improvement of psychotic symptomatology in schizophrenia patients (Risch *et al.*, 2001; Buchanan *et al.*, 2002; Friedman *et al.*, 2002; Howard *et al.*, 2002; Stryjer, 2002, 2003), in this study the intention was to determine for the first time whether donepezil augmentation of clozapine monotherapy in schizophrenia patients would improve psychotic symptomatology.

PATIENTS AND METHODS

Study population

The study was carried out at the Beer Yaakov Mental Health Center, a large state run academic psychiatric hospital. The study was approved by the local Helsinki Ethics Committee, and all patients and their family members received full explanation of the study before the patient provided written informed consent. Candidates for study participation were assessed by two certificate board psychiatrists who made the diagnosis of schizophrenia according to DSM-IV criteria. In order to qualify for eligibility to participate in the study, patients were required to be in the age range 18–50 years, to have been treated with a stable tolerated dose of clozapine as monotherapy for a minimum period of 6 months and still present active psychotic symptomatology, and to have a history of nonresponse to two different antipsychotic drugs of different classes at equivalent chlorpromazine dose of 1000 mg for a period of at least 8 weeks. Patients with current substance abuse, organic brain disorder, mental retardation, history of severe head trauma, or any medical condition that may exacerbated by donepezil, such as obstructive pulmonary disease, were excluded. Eight patients were recruited (5 males, 3 females) for study participation. The age of subjects was 26–42 years old. Only six patients completed the study, two patients were lost to follow up after the completion of the first phase (8 weeks).

The demographic characteristics of the six patients who completed the study were as follows: four males and two females, age (34.8 ± 5.4 years), disease duration (7.6 ± 3.5 years), clozapine dose (466.6 ± 51.6 mg/day), duration of clozapine treatment (3.08 ± 1.1 years).

Study design

Subjects participating were randomly assigned to an 18-week trial of donepezil or placebo added to clozapine monotherapy in a crossover design separated by a 2-week washout period. At baseline four patients were allocated randomly to donepezil and four patients to placebo. The clozapine dose was maintained unchanged according to study protocol and no additional medication was added during the 18 weeks study. Either donepezil or placebo was given on a once a day schedule at a dose of 5 mg/day for the first 4 weeks and at 10 mg/day for the following 4 weeks. After this initial phase, there was a 2-week washout period of the medication after which the same regimen was crossed over at the same dose and for the same period (another 8 weeks) either to donepezil or placebo according to patient randomization. During the 2 weeks washout period only placebo or donepezil were stopped, while clozapine was continued throughout these 2 weeks washout period. The patients and the raters were not blind to the cross-over nature of the trial. Pill counting was performed each week in order to confirm compliance. All patients underwent a comprehensive physical and psychiatric evaluation that included blood levels for thyroid function, vitamin B12, folic acid, electrolytes including calcium, complete blood count, renal and liver functions and EKG. During the trial, clozapine dosage was maintained unchanged and the addition of other medications was not permitted unless absolutely necessary for clinical reasons. Blood count was followed once a month according to Israel Ministry of Health guidelines for the treatment with clozapine.

Evaluations

All patients were clinically assessed by a blinded rater who performed the clinical evaluations at baseline and after 4 weeks, 8 weeks, 10 weeks, 14 weeks and 18 weeks of the study. These evaluations included the positive and negative symptom scale (PANSS) (Kay *et al.*, 1987), Calgary depression scale (CDS) (Addington *et al.*, 1993), Simpson-Angus scale (SAS) (Simpson and Angus, 1970) and the clinical global impression—improvement (CGI-I) scale (Guy, 1976). The clinical global impression—severity of illness (CGI-S) (Guy, 1976) was performed at baseline, 8 weeks, 10 weeks and 18 weeks. Unfortunately due to the preliminary and complex nature of the study, cognitive function was not assessed.

Statistical analysis

A two-tailed *t*-test was used for comparison of changes in outcome measures at baseline and week 8 (endpoint of phase-baseline of phase) for placebo phase versus corresponding changes in the donepezil phase. All the results are expressed as mean $\pm$ SD.

RESULTS

No significant difference was noted in total PANSS scores when donepezil was compared with placebo, ($16.7\% + 12.97\%$ vs $3.20\% + 13.94\%$ respectively, $p = 0.18$). However, three patients improved (>15%) in total PANSS scores (37.03%, 16.6% and 25.33%) during the donepezil treatment phase, while only one patient improved (20.87%) during the placebo phase.

There were no statistical differences between the placebo and donepezil phase in CGI-I ($p = 0.23$), CGI-S ($p = 0.116$), SAS ($p = 0.374$) and Calgary depression scale ($p = 0.305$) scores. The results reflect the changes in all patients during the donepezil phase versus the placebo phase, irrespective of whether this was during week 0–8 or week 10–18.

Of the two patients who completed the first phase (8 weeks), one completed the placebo phase and demonstrated worsening of PANSS scores (baseline 89 and endpoint 93). The second patient completed the donepezil phase and scored 79 at baseline and 58 at endpoint, indicating in these two patients an improvement in the donepezil phase in one patient and worsening under placebo in the second patient.

DISCUSSION

In our study no significant improvement was observed in the overall measure of psychosis of the patients investigated. This is in concordance with other reports in which donepezil did not improve psychotic symptomatology in schizophrenia patients (Risch *et al.*, 2001; Buchanan *et al.*, 2002; Friedman *et al.*, 2002; Howard *et al.*, 2002; Stryjer, 2002, 2003). Recent evidence suggests that muscarinic/cholinergic inhibition of brain dopaminergic activity may be a useful principle in the development of novel antipsychotic medication (Ichikawa *et al.*, 2002a). Cholinergic enhancement by antipsychotic medication differs in potency according to the medication. In a study by Shirazi-Southall *et al.* (2002), clozapine and olanzapine produced robust increases in acetylcholine up to 1500% and 500%, respectively, in the rat hippocampus, while the neuroleptic medications haloperidol, thioridazine and chlorpromazine, as well as the atypical antipsychotic medications risperidone and ziprasidone, produced modest increases in acetylcholine of about 50%–100%. Whether more robust cholinergic enhancement by clozapine in comparison to other antipsychotic medication (Shirazi-Southall *et al.*, 2002; Ichikawa *et al.*, 2002b) accounts for its improved efficacy, at least in part, remains unclear. However, combination of donepezil with clozapine did not lead to further improvement of psychosis. This is similar to the lack of effect of donepezil when combined with risperidone and olanzapine (Buchanan *et al.*, 2002; Friedman *et al.*, 2002).

During the study, the white blood count was monitored once a month according to Ministry of Health guidelines for clozapine treatment. No interactions between donepezil and clozapine have been reported that may increase the risk for agranulocytosis. While an increased risk for seizures exists especially since the risk of seizures, while very rare, does exist with donepezil (Babic and Zurak, 1999), we remain unaware of any report of seizures induced by the combination of clozapine and donepezil. For the duration of the study, no worsening or any emergence of extrapyramidal side effects was observed. This is not unexpected considering the increased acetylcholine in the basal ganglia induced by the cholinesterase inhibitor donepezil.

These study observations are supported by other reports in which donepezil was well tolerated (Aarsland *et al.*, 2002; Bergman and Lerner, 2002) and did not worsen Parkinsonism in patients with Parkinson disease (PD). Interestingly, it may even improve Parkinsonism in PD (Mori, 2002; Werber and Rabey, 2001).

Since reports regarding the management of the subgroup of patients who are either partial or non responders to clozapine monotherapy remain limited (e.g. Buckley *et al.*, 2001) it is suggested that further study on augmentation therapy to this 'difficult to treat' subgroup of treatment-resistant schizophrenia patients is of considerable importance. This approach is further substantiated by the current lack of established augmentation strategies to clozapine therapy, except for the double-blind, placebo-controlled study performed by Shiloh *et al.* (1997) in which the selective D2 antagonist sulpiride was added to clozapine in clozapine-resistant patients with encouraging results. While it is recognized that the small sample of patients is a major weakness of this study and may limit definitive conclusions that may be assumed from the study results, based on some of our observations, it is suggested that donepezil may be considered as an option for augmentation therapy in clozapine resistant schizophrenia patients. Further large scale, double-blind placebo-controlled donepezil add-on studies in clozapine resistant patients are certainly warranted.

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