PRIORITY COMMUNICATION

Galantamine Improves Cognition in Schizophrenic Patients Stabilized on Risperidone

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Background: *Cognition in schizophrenia is impaired in a variety of cognitive domains. Galantamine, a cholinesterase inhibitor with putative nicotinic agonist-like effects, improves cognition in Alzheimer's patients.*

Methods: *Sixteen schizophrenic or schizoaffective patients stabilized on risperidone were administered galantamine (n=8) or placebo (n=8) in a randomized, double-blind trial. The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) assessed changes in cognitive performance over an eight-week treatment interval.*

Results: *Clinical symptoms improved in both groups during the trial with no evidence that galantamine exacerbated extrapyramidal symptoms. Patients treated with galantamine experienced an overall improvement in cognitive performance (RBANS Total scale score; galantamine = 12.1 ± 12.8 SD, placebo = .5 ± 13.5,* $t = 2.32$, $p < .04$*). Confidence intervals suggest that RBANS Attention and Delayed Memory subscale performance was robustly improved in galantamine patients by approximately one standard deviation, effectively normalizing cognitive performance in these domains.*

Conclusions: *Adjunctive treatment with galantamine improves memory and attention in patients with schizophrenia who are stabilized on risperidone, providing the opportunity to improve functional outcome in these patients.*

Key Words: Memory, attention, antipsychotic, cholinesterase inhibitor, neuropsychology, drug trial

Cognition in schizophrenia is impaired in a variety of domains including immediate memory, short-term memory, attention, noetic learning and executive functioning (Gold et al 1999b; Goldberg et al 1990; Green et al 2000). Significant improvements in these cognitive domains have been observed with antipsychotic medications, including the second generation agent risperidone (Purdon 1999, 2000; Harvey and Keefe 2001). One of the few pharmacologic approaches demonstrated to improve cognition in cognitively impaired patients is the use of agents that facilitate activity at cholinergic synapses (Cummings 2000). Most studies have indicated that cholinesterase inhibitors are modestly effective in improving cognitive impairments in Alzheimer's Disease (Cummings 2000; Knapp et al 1994; Rogers et al 1998; Morris et al 1998). Galantamine is a cholinesterase inhibitor and nicotinic allosteric agonist which improves cognitive performance in Alzheimer's patients (Raskind et al 2000), and has shown potential as an adjunctive treatment for schizophrenia in an open label trial (Allen and McEvoy 2002).

In this study of schizophrenic or schizoaffective patients stabilized on risperidone, we investigated adjunctive therapy with galantamine in a randomized, double-blind, placebo-controlled trial.

Methods and Materials

Sixteen males and one female stabilized on risperidone as their only antipsychotic medication for a minimum period of four weeks were interviewed by two separate clinicians prior to being randomly assigned to one of the treatment arms. Subjects ranged in age from 26–55 years, all met DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder, depressed type, and all but one were smokers. Subjects were excluded if there was documented history of intolerance to cholinesterase inhibitors, DSM-IV substance dependence/abuse, or use of any anticholinergic or psychotropic medication other than risperidone within the 30 days prior to enrollment in the protocol or during the study. The protocol was reviewed and approved by the Central Texas Veterans Health Care System institutional review board. All patients provided written informed consent before participation in the study and were paid a small honorarium for travel and time.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al 1998) was the primary outcome instrument for the study. The RBANS provides an overall cognitive function score (RBANS total scale score) as well as five index scores: immediate memory (IM), visuospatial/constructional (VC), language (L), attention (AT), and delayed memory (DM). Clinical status was assessed using the Positive and Negative Symptom Scale (PANSS; Kay et al 1989), Clinical Global Impressions Scale (CGI), Abnormal Involuntary Movement Scale (AIMS; Guy 1976), and the Simpson-Angus Scale (SAS; Simpson and Angus 1970). Secondary measures of cognition included the Conner's Continuous Performance Test (CPT; Cornblatt et al 1988), Object Matching Memory Test (OMMT; Conway and Dewhurst 1995; Danion et al 1999), Tower of Toronto Puzzle Test (TOT; Saint-Cyr et al 1988; Salgado et al 2000), and the Unirhinal Olfactory Acuity test (UOA; Purdon and Flor-Henry 2000). Subjects were randomly and blindly assigned to receive treatment with galantamine or placebo in addition to their established risperidone treatment (either 4 or 6 mg daily). Galantamine tablets were over-encapsulated to be indistinguishable from placebo. All patients were stable on the entry dose of risperidone for at least 30 days and did not receive additional psychotropic medications during the trial. The starting dose of galantamine was 8 mg daily (administered 4 mg twice daily), with the daily dose increasing at 2-week intervals to 16 mg and then 24 mg (each dosage administered in equal morning and evening doses). Clinical assessments (PANSS, CGI, AIMS, SAS) were administered on day 1, 8, 15, 29, 50 and 57. Cognitive tests were performed on day 1 or 2 and either on day 50 (TOT) or day

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57 (RBANS, CPT, UOA). All patients were provided a smoking break prior to RBANS testing.

Statistical Analysis

The primary outcome measure for the study was change in the RBANS total scale score from baseline to the final treatment. A *t*-test was used to compare change from baseline using a last observation carried forward design. We also repeated the RBANS total scale score *t*-test after excluding one subject that completed the second RBANS testing with less than four weeks of treatment, tested for unequal variances, and confirmed the parametric testing with nonparametric analysis. Confidence intervals were used to define additional changes during the trial, including those in secondary outcome measures.

Results

Fourteen out of seventeen patients completed initial and final RBANS tests, and were included in the last observation carried forward analysis. One patient in the placebo group was disqualified because of use of psychotropic medications, one patient in the placebo group withdrew because of persistent diarrhea, and one patient in the placebo group withdrew because of re-emergence of psychotic symptoms that prevented further testing. There were no group differences for age (galantamine = 48.3 years ± 6.9 SD; placebo = 46.8 ± 8.8), average risperidone dose (galantamine = 5.75 mg ± 1.3; placebo = 5.25 ± 1.0) or months on risperidone prior to randomization (galantamine = 28.2 months ± 19.0; placebo = 35.6 ± 34.1). Galantamine was well tolerated with no evidence for severe side effects. In addition, there was evidence for improved AIMS scores in the galantamine but not in the placebo group (Table 1). There was not a significant change in the number of cigarettes smoked from the first to the last week for either control or galantamine group. At the beginning of the trial, both groups of patients scored a mean of 87 on the RBANS Total scale score. At the end of the trial, the galantamine group scored 99 ± 24 SD, while the placebo group scored 82 ± 20.

Compared to placebo, galantamine subjects had more consistent improvement in RBANS performance over the trial period (galantamine = 12.1 ± 12.8 SD, placebo = −.5 ± 13.5, $t = 2.32$, $p < .04$). Five of eight galantamine subjects experienced a > 12 point improvement in overall cognitive performance (−4, −2, 0, 13, 16, 19, 25, 30), while none of the patients receiving placebo evidenced such improvement (−8, −7, −5, 2, 5, 10). When data from the single patient that withdrew from the study and completed both RBANS tests with less than four weeks of treatment was excluded (galantamine arm), there was still a significant elevation of RBANS total scale score ($t = 2.48$, $p < .032$). Confidence intervals (see Table 1) suggest that there was no change in RBANS performance during the trial for patients in the placebo group, but that galantamine improved Total, Attention and Delayed Memory RBANS scores. PANSS total scale scores improved for both groups during the trial, with no evidence for a selective effect of galantamine. CGI and SAS changes during the treatment were in the direction of improvement for the galantamine but not the placebo group. There was no evidence for galantamine effects on the UAO, TOT or CPT tests. Tests for unequal variances using the Levene and Bartlett tests were negative, and use of an unequal variance t-test did not alter the significant result achieved for the RBANS Total scale score ($t = 2.33$, $p < .040$). Due to the small sample size, the wide range of responses and high level of variances, we repeated the key statistical tests using the nonparametric Van der Waerden test for normalcy of quartiles. For the RBANS data, the Van der Waerden chi square approximation at a $p < .05$ level supported all of the above statistical findings, suggesting that the skewness of the data was unlikely to have biased the statistical results.

Table 1. Change from Baseline (T_2-T_1)

	Galantamine			Placebo				
	Mean Change	SD	Conf. Interval	Mean Change	SD	Conf. Interval	*t*	*p*
RBANS Total	12.1	12.8	1.4, 23	−.5	7.3	−8, 7	2.32	.04
IM	13.4	19.4	−2.9, 30	4.7	12.7	−8.7, 18	1.01	.33
VC	2.4	16.1	−11, 16	2.3	10.3	−8.5, 13	.01	.99
L	4.2	11.3	−5.2, 14	−1.2	6.0	−7.4, 5.1	1.16	.27
AT	10.9	12.3	.6, 21	−4.8	9.4	−15, 5.0	2.70	.02
DM	12.5	14.5	.4, 25	−5.8	13.1	−20, 8.1	2.46	.03
CGI	−.57	.78	−1.3, .2	.0	.6	−.6, .6	1.45	.17
AIMS	−2.7	1.7	−4.0, −1.2	.2	−.7	−3.3, 1.9	1.66	.14
SAS	−3.5	4.5	−7.3, .3	.0	2.6	−2.6, 2.6	1.87	.09
PANSS Total	−12.2	14.4	−24.3, −.2	−13.5	4.7	−21.2, −9.7	.58	.57
POS	−4.3	6.0	−9.2, .7	−4.0	4.2	−8.4, .4	.10	.92
NEG	−3.3	4.4	−7.0, −.5	−2.5	2.9	−5.5, .5	.38	.71
CPT COM	−3.8	5.2	−4.8, 4.0	−1.7	3.4	−5.3, 1.9	.36	.72
OMMT PE	−2.7	6.4	−7.9, 2.7	−1.8	3.9	−5.9, 2.2	.53	.60
TOT	−16	15.6	−32, .4	−5.5	16.1	−21, 4.5	1.15	.28
UOA-Left	.29	1.6	−1.2, 1.8	.67	2.0	−1.4, 2.7	.38	.71
UOA-Right	2.14	3.0	−.7, 4.9	.33	3.14	−2.2, 3.9	.80	.44

RBANS, TOT, OMMT and UOA data are from 8 galantamine and 6/8 placebo patients completing baseline and final testing. Other measures are last observation carried forward for 8 subjects/group.

RBANS, Repeatable Battery for Assessment of Neuropsychological Status; IM, immediate memory; VC, verbal comprehension; L, language; AT, attention; DM, delayed memory (high values = improvement); CGI, Clinical Global Impressions (low values = improvement); AIMS, Abnormal Involuntary Movements (low values = improvement); SAS, Simpson-Angus Scale (low values = improvement); PANSS, Positive and Negative Symptom Scale (low values = improvement); CPT COM, Continuous Performance Task Errors of Commission (low values = improvement); OMMT PE, Object Matching Memory Test Percent Performance Errors (low values = improvement); TOT, Tower of Toronto moves to solve (low values = improvement); UOA-Left, Unirhinal Olfactory Acuity Test Left Nostril (high values = more sensitivity); UOA-Right, Unirhinal Olfactory Acuity Test Right Nostril (high values = more sensitivity).

Discussion

The present data suggest that an eight-week adjunctive treatment with galantamine in patients being medicated with risperidone improved selected aspects of cognition. This finding was not due to unequal clinical deterioration of the placebo group because overall clinical symptoms assessed by the PANSS improved in both groups during the trial. The most striking finding from the present study was an improvement in attention and delayed memory in patients receiving galantamine. Treatment of cognitive deficits with antipsychotics by themselves have resulted in modest benefits (Harvey and Keefe 2001), and these benefits have been achieved over longer treatment periods than the present investigation. The magnitude of the improvement in overall cognitive function by adjunctive galantamine compares favorably with previous attempts to treat cognitive dysfunction in schizophrenia with antipsychotics alone.

The present study illustrates the utility of the RBANS in drug trials. The RBANS has two equivalent versions and was specifically designed for test-retest usage (Randolph et al 1998). A score of 85 has been reported to represent a 1 SD deficit in RBANS total scale score (Gold et al 1999a). Subjects in the present study scored 87 before randomization, indicating they were performing in the borderline to low average range. This modest level of impairment at the beginning of the trial may reflect the fact that these patients had already responded to risperidone (Joober et al 2002; Weickert et al 2003). It is interesting that galantamine treatment further normalized cognition in these subjects.

In animals with memory and learning deficits, treatment with cholinesterase inhibitors including galantamine can reverse cognitive deficits (Van Dam et al 2005). Open-label trials of cholinesterase inhibitors have generally yielded evidence supporting cognitive facilitation in schizophrenic patients (Buchanan et al 2002; Howard et al 2002; Lenzi et al 2003; Mendelsohn et al 2004; Stryjer et al 2003; Allen and McEvoy 2002). Some trials of cholinesterase inhibitors, however, have not demonstrated this benefit (Friedman et al 2002). Galantamine's cognitive effects may be accentuated by its nicotinic allosteric agonist action, which can improve attention and memory (Kihara et al 2004; Maelicke et al 2001; Hernandez and Terry, Jr. 2005). Furthermore, galantamine appears to more powerfully elevate frontal cortical dopamine levels compared to cholinesterase inhibitors such as donepezil (Zhang et al 2004; Geerts et al 2005). This biological effect may be significant, since frontal dopaminergic deficits have been proposed to underlie cognitive impairment in schizophrenia (Goldberg and Weinberger 2004; Seamans and Yang 2004). A net improvement of dopaminergic function produced by a combination of cholinergic and nicotinic actions may also explain the fact that we did not observe exacerbation of extrapyramidal symptoms with galantamine.

In summary, we provide initial evidence that galantamine can be a beneficial adjunct to risperidone to improve short-term memory and attention in patients with schizophrenia. Development of treatments that normalize cognitive deficits in patients with schizophrenia is a high priority clinical goal because it is recognized that this strategy is likely to result in improvements in psychosocial function (Gold et al 1999b; Green 1996; Green et al 2000). Although the present study size was limited, the results suggest that galantamine has a robust effect on memory and attention with potential to improve functional outcome in schizophrenic patients. (Rockwood et al., 2001).

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