Brief Report

Enhancement of Cognitive Performance in Schizophrenia by Addition of Tandospirone to Neuroleptic Treatment

Tomiki Sumiyoshi, M.D., Ph.D.
Mié Matsui, Ph.D.
Shigeru Nohara, M.D., Ph.D.
Ikiko Yamashita, M.Ed.
Masayoshi Kurachi, M.D., Ph.D.
Chika Sumiyoshi, Ph.D.
Karu Jayathilake, Ph.D.
Herbert Y. Meltzer, M.D.

Objective: The goal of this study was to evaluate the effects of the addition of tandospirone, a serotonin-1A (5-HT_{1A}) agonist, to ongoing treatment with typical antipsychotic drugs, on two cognitive domains that are relevant to functional outcome in patients with schizophrenia.

Method: Twenty-six patients with schizophrenia who were receiving stable doses of typical antipsychotics were randomly assigned to adjunctive treatment with 30 mg/day of tandospirone or placebo for 6 weeks. Executive function and verbal memory as well as psychopathology were assessed at baseline and after 6 weeks.

Results: Both cognitive measures improved significantly in the patients who received tandospirone; subjects who did not receive tandospirone showed no change. There was no significant change in psychopathology ratings in either group.

Conclusions: The results suggest the usefulness of 5-HT_{1A} agonists for enhancing some types of cognitive performance and possibly social and work function in patients with schizophrenia.

(Am J Psychiatry 2001; 158:1722–1725)

Cognitive functions such as memory, executive function, and attention are impaired in patients with schizophrenia (1) and are predictive of vocational and social outcome (2). Among the domains of cognitive function, secondary verbal memory and executive function have been suggested to be major predictors of functional outcomes in patients with schizophrenia (2, 3).

Although typical antipsychotic drugs such as haloperidol have minimal influence on cognitive function, recent studies (3, 4) have shown that atypical antipsychotic drugs such as clozapine, risperidone, and olanzapine enhance cognitive performance in patients with schizophrenia. Facilitation of cortical dopaminergic and cholinergic output may contribute to the ability of these agents to improve cognitive function (3, 5).

Serotonin-1A (5-HT_{1A}) receptor agonists have been shown to enhance dopaminergic and cholinergic neurotransmission in the cortex and/or hippocampus (6, 7). There is also evidence from postmortem studies indicating abnormalities in 5-HT_{1A}-receptor-mediated transmission in the cortical region in patients with schizophrenia (8). We have previously reported (9) that the azapirone derivative tandospirone, a selective 5-HT_{1A} agonist that is used as an anxiolytic (10), improved logical memory and verbal paired associates in patients with schizophrenia in an open clinical trial.

The aim of this study, therefore, was to determine whether the addition of tandospirone to treatment with typical antipsychotic drugs has a beneficial influence on executive function and secondary verbal memory in patients with schizophrenia.

Method

Participants for this study were 26 outpatients meeting DSM-IV criteria for schizophrenia treated at Toyama Medical and Pharmaceutical University Hospital. All of the subjects had been treated with small-to-moderate stable doses of typical antipsychotic drugs (haloperidol, N=23; sulpiride, N=2; pimozide, N=1) and biperiden as an antiparkinsonian agent for at least 3 months (Table

TABLE 1. Demographic and Clinical Data for Patients With Schizophrenia Treated With Typical Neuroleptics Plus Either Tandospirone (N=15) or Placebo (N=11)

	Patients Given Placebo		Patients Given Tandospirone		Analysis of Variance (df=1, 24)			
					Group Effect		Time-by-Group Interaction	
Variable	Mean	SD	Mean	SD	F	p	F	p
Age (years)	31.8	9.4	27.8	6.3	1.53	n.s.		
Duration of illness (years)	7.5	5.4	6.3	4.3	0.40	n.s.		
Age at onset (years)	24.1	10.8	21.5	4.7	0.54	n.s.		
Education (years)	13.6	2.2	12.5	1.7	1.87	n.s.		
Baseline WAIS-R scores								
Vocabulary	8.7	4.5	7.1	3.1	0.82	n.s.		
Block design	9.3	3.4	8.8	3.6	0.14	n.s.		
Neuroleptic dose (mg/day)[a]	215	230	250	245	0.12	n.s.		
Biperiden dose (mg/day)	3.9	2.4	3.6	1.8	0.07	n.s.		
BPRS								
Total					0.46	n.s.	0.00	n.s.
Baseline	18.9	8.7	16.8	9.0				
6 weeks	16.6	8.9	14.3	9.3				
Positive subscale					1.71	n.s.	0.05	n.s.
Baseline	6.4	3.4	4.4	4.0				
6 weeks	5.3	4.5	3.6	3.8				
Negative subscale					0.77	n.s.	0.21	n.s.
Baseline	4.2	3.0	5.4	3.4				
6 weeks	3.5	3.3	4.4	2.8				
Simpson-Angus Rating Scale					0.00	n.s.	0.02	n.s.
Baseline	1.4	1.6	1.5	2.2				
6 weeks	1.4	2.1	1.4	1.6				
Wisconsin Card Sorting Test								
Number of categories[b]					0.25	n.s.	7.17	0.02
Baseline	4.6	1.7	3.5	2.0				
6 weeks	4.6	2.1	5.1	0.9				
Percent perseverative errors					0.15	n.s.	0.88	n.s.
Baseline	30.1	24.3	33.3	24.4				
6 weeks	37.0	22.5	28.7	17.2				
Wechsler Memory Scale—Revised verbal memory composite[c]					0.24	n.s.	10.82	0.003
Baseline	48.1	18.1	46.1	19.5				
6 weeks	53.1	20.3	62.4	18.7				

[a] Chlorpromazine equivalents.
[b] Significant difference between baseline and 6 weeks for tandospirone patients ($F=16.94$, $df=1, 24$, $p<0.001$).
[c] Significant difference between baseline and 6 weeks for tandospirone patients ($F=53.14$, $df=1, 24$, $p<0.0001$).

1). Diagnosis was made by two experienced psychiatrists using the Structured Clinical Interview for DSM-IV based on the patient's current mental status and a review of all medical records. Patients with an axis I diagnosis other than schizophrenia were excluded. Exclusionary criteria also included a history of any alcohol or substance abuse, epilepsy, brain damage, or neurological disorders and the presence of cardiovascular or metabolic disease. After complete description of the study to the subjects, written informed consent was obtained.

At baseline, executive function and verbal memory were evaluated with the Wisconsin Card Sorting Test (the number of categories and the percent of perseverative errors) (11) and the verbal memory composite score (logical memory I and verbal paired associates I) from the Wechsler Memory Scale—Revised (WMS-R) (12), respectively, by a well-trained clinical psychologist who was blind to the medication status of the subjects. The 18-item version of the Brief Psychiatric Rating Scale (BPRS) (0–6 scale) (13) and the Simpson-Angus Rating Scale (14) were completed at the time of the psychological testing by experienced clinical psychiatrists who were blind to the subjects' medication status and to the results of the neuropsychological assessment. The intraclass correlations for these measures were higher than 0.80. For evaluation of baseline verbal and performance IQ, the WAIS-R Vocabulary and Block Design subtests were performed.

Patients were randomly assigned to receive tandospirone, 30 mg/day (9, 10) (10 mg t.i.d. in powder form mixed with lactose), or placebo (lactose alone) for 6 weeks. Fifteen patients (nine men and six women) were given tandospirone; 11 patients (six men and five women) were given placebo. All other psychotropic medications were continued unchanged.

Scores on the Wisconsin Card Sorting Test, WMS-R, BPRS (total, positive subscale, and negative subscale) and Simpson-Angus Rating Scale were obtained again after 6 weeks of tandospirone or placebo administration. The changes in the scores of these measures for the two groups were compared by using repeated measures analysis of variance with treatment (tandospirone versus placebo) as a between-subject factor and time (baseline versus week 6) as a within-subject factor. Our main interest was in finding any existing interaction effects of treatment over time; subsequent post hoc tests were also conducted. Significance was considered when the p value was less than 0.05.

Results

All 26 patients completed the 6-week trial; there was no clinically significant side effect attributable to the addition of tandospirone. The mean age, duration of illness, age at onset of illness, education, scores on the WAIS-R subtests, and doses of neuroleptics (in chlorpromazine equivalents) or biperiden did not differ significantly between the two groups (Table 1). There were no significant group differences in the baseline scores on the BPRS (total, positive

subscale, and negative subscale), Simpson-Angus Rating Scale, Wisconsin Card Sorting Test (the number of categories and percent of perseverative errors) or WMS-R verbal memory composite score (Table 1).

Significant time-by-group interaction effects were noted for the Wisconsin Card Sorting Test categories and WMS-R verbal memory composite score: patients who had received tandospirone performed better at 6 weeks than at baseline for these measures (with effect sizes of 0.63 and 0.70, respectively), but no significant change was found for patients receiving placebo (Table 1). There was no significant time-by-group interaction effect or main effect of time for the BPRS (total, positive subscale, negative subscale), Simpson-Angus Rating Scale, and Wisconsin Card Sorting Test percent of perseverative errors.

Discussion

The addition of tandospirone to ongoing treatment with typical antipsychotic drugs for 6 weeks was found to improve executive function, as indicated by improvement in the Wisconsin Card Sorting Test categories, and verbal memory without causing significant changes in psychopathology or extrapyramidal symptoms in patients with schizophrenia. The effect sizes of both cognitive measures were in the moderate range. The absence of improvement in the group given placebo rules out the possibility of a practice effect. The lack of change in psychopathology suggests that the improvement in the cognitive measures could result from a primary effect on cognition and was not secondary to decreased positive or negative symptoms. The observed effect of tandospirone on verbal memory confirms the results of our previous 4-week trial (9).

Pharmacological manipulations of dopamine, norepinephrine, acetylcholine, or glutamate neurotransmitter systems have been suggested to demonstrate cognition-enhancing potential in schizophrenia (15). The effectiveness of 5-HT_{1A} agonists for ameliorating cognitive impairment is consistent with the 5-HT_{1A} partial agonist properties of several atypical antipsychotics, including clozapine, quetiapine, and ziprasidone (16, 17). The present findings may have implications for improving cognition and possibly social and work function in patients with schizophrenia who continue to receive typical antipsychotic drugs.

Some limitations of the present study need to be considered. First, this is a small study of relatively short duration, raising the possibility of a type II error on some measures examined. A longer trial with a larger number of subjects may have detected significant changes in, for example, psychopathology. Second, it would be worthwhile to determine if improvement persists or even increases with a longer duration of treatment.

Received Jan. 12, 2001; revision received March 30, 2001; accepted April 23, 2001. From the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University School of Medicine, Toyama, Japan; and the Department of Psychiatry, Vanderbilt University School of Medicine. Address reprint requests to Dr. Sumiyoshi, Department of Psychiatry, Division of Psychopharmacology, Psychiatric Hospital at Vanderbilt, Vanderbilt University Medical Center, 1601 23rd Ave. South, Suite 306, Nashville, TN 37212; tomiki.sumiyoshi@mcmail.vanderbilt.edu (e-mail).

Supported by a grant from the Japan Research Foundation for Clinical Pharmacology, a fellowship from the Ministry of Education and Science of Japan, and a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (Dr. Sumiyoshi).

The authors thank Drs. Kenzo Kurokawa and Takashi Uehara for their contributions.

References

1. Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N: Generalized cognitive deficits in schizophrenia: a study of first-episode patients. Arch Gen Psychiatry 1999; 56:749–754
2. McGurk SR, Meltzer HY: The role of cognition in vocational functioning in schizophrenia. Schizophr Res 2000; 45:175–184
3. Meltzer HY, McGurk SR: The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull 1999; 25:233–255
4. Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, Breier A, Tollefson GD: Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. Arch Gen Psychiatry 2000; 57:249–258
5. Parada MA, Hernandez L, Puig de Parada M, Rada P, Murzi E: Selective action of acute systemic clozapine on acetylcholine release in the rat prefrontal cortex by reference to the nucleus accumbens and striatum. J Pharmacol Exp Ther 1997; 281: 582–588
6. Rasmusson AM, Goldstein LE, Deutch AY, Bunney BS, Roth RH: 5-HT_{1A} agonist +/-8-OH-DPAT modulates basal and stress-induced changes in medial prefrontal cortical dopamine. Synapse 1994; 18:218–224
7. Koyama T, Nakajima Y, Fujii T, Kawashima K: Enhancement of cortical and hippocampal cholinergic neurotransmission through 5-HT_{1A} receptor-mediated pathways by BAY x 3702 in freely moving rats. Neurosci Lett 1999; 265:33–36
8. Sumiyoshi T, Stockmeier CA, Overholser JC, Dilley GE, Meltzer HY: Serotonin$_{1A}$ receptors are increased in postmortem prefrontal cortex in schizophrenia. Brain Res 1996; 708:209–214
9. Sumiyoshi T, Matsui M, Yamashita I, Nohara S, Uehara T, Kurachi M, Meltzer HY: Effect of adjunctive treatment with serotonin-1A agonist tandospirone on memory functions in schizophrenia. J Clin Psychopharmacol 2000:386–388
10. Murasaki M, Mori A, Endo S, Takemasa K, Hasegawa K, Kamijima K, Yagi G, Kudo Y, Nakajima T, Saito M, Nishimura T, Kawakita Y: [Efficacy of a new anxiolytic, tandospirone (SM-3997), on neurosis—a comparative double-blind study with diazepam.] Rinshô Hyôka (Clinical Evaluations) 1992; 20:295–329 (Japanese)
11. Nelson HE: A modified card sorting test sensitive to frontal lobe defects. Cortex 1976; 12:313–324
12. Sugishita M: The Japanese Version of the Wechsler Memory Scale—Revised. Tokyo, Nihon Bunka Kagakusha, 2001
13. Rhoades HM, Overall JE: The semistructured BPRS interview and rating guide. Psychopharmacol Bull 1988; 10:101–104
14. Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970; 212:11–19

15. Friedman JI: Specific cognitive enhancers, in Cognition in Schizophrenia: Impairments, Importance, and Treatment Strategy. Edited by Sharma T, Harvey P. New York, Oxford University Press, 2000, pp 303–331
16. Newman-Tancredi A, Gavaudan S, Conte C, Chaput C, Touzard M, Verriele L, Audinot V, Millan MJ: Agonist and antagonist actions of antipsychotic agents at 5-HT_{1A} receptors: a [^{35}S]GTPγ-S binding study. Eur J Pharmacol 1998; 355:245–256
17. Ichikawa J, Ishii H, Bonaccorso S, Fowler WL, O'Laughlin IA, Meltzer HY: 5-HT_{2A} and D_2 receptor blockade increases cortical DA release via 5-HT_{1A} receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem 2001; 76:1521–1531