

The Effect of Risperidone on Cognitive Functioning in a Sample of Asian Patients with Schizophrenia in Singapore

L Chua, S A Chong, E Pang, V P Y Ng, Y H Chan

ABSTRACT

Objective: To evaluate the effect of risperidone treatment on the cognitive functioning in a group of Asian patients with schizophrenia.

Method: Patients with DSM-III-R schizophrenia were recruited from Woodbridge Hospital. Several domains of cognitive functions were assessed at baseline before washout, at 8 weeks and 6 months after initiation of treatment on risperidone. Clinical outcome was assessed on the Positive and Negative Syndrome Scale (PANSS).

Results: Significant improvements were found in verbal fluency and certain aspects of memory 8 weeks after risperidone treatment. There were significant improvements in executive and memory functioning after 6 months. Improvements were also noted in attention and perceptual/motor processes although these did not reach significant levels. Treatment on risperidone also resulted in significant reduction in the PANSS score.

Conclusion: Our results are consistent with those found in other studies in which risperidone was shown to be effective in improving several aspects of cognitive functioning. There were corresponding effectiveness in treating positive and negative symptoms of schizophrenia. Such improvements can have positive implications on vocational and social functioning.

Keywords: risperidone, cognitive functioning, schizophrenia, Asian

Singapore Med J 2001 Vol 42(6):243-246

INTRODUCTION

Neurocognitive deficits are now recognised as part of the fundamental disturbances in schizophrenia^(1,2). Patients with schizophrenia have widespread, multifaceted impairments in many domains of cognitive functioning, including executive function, concentration, perceptual/motor processing, vigilance, verbal learning and memory, verbal and spatial working memory, and

semantic memory⁽³⁻⁶⁾. These cognitive impairments are important in predicting functional outcomes such as work status, activities of daily living, community outcome, social problem solving and psychosocial skill acquisition⁽⁷⁻⁹⁾.

While typical neuroleptics have been effective in reducing positive symptoms of schizophrenia, there is no conclusive evidence that they treat these cognitive impairments⁽¹⁰⁾. Acute treatment with typical neuroleptics may worsen some aspects of attention⁽¹¹⁻¹²⁾. The majority of studies showed that typical neuroleptics do not improve the impairments in short-term memory⁽¹³⁾. The propensity of typical neuroleptics to cause extrapyramidal side-effects often necessitates the addition of anticholinergic drugs which also cause significant memory impairment⁽¹⁵⁾.

The newer atypical neuroleptics have been reported to alleviate some of these cognitive impairments⁽¹⁶⁾. Various studies have shown that risperidone has a positive effect on certain aspects of cognitive functioning like vigilance⁽¹⁷⁾ and memory⁽¹⁸⁾.

This study evaluated the effect of risperidone on cognitive functioning in a sample of Asian patients treated for schizophrenia at Woodbridge Hospital.

METHOD

Patients who participated in the study were conversant in the English language and were able to give informed consent. They fulfilled the DSM-III-R criteria for schizophrenia and were from a group of patients who were undergoing a concurrent open study which assessed the efficacy and safety of risperidone⁽¹⁹⁾. These patients were between 18 and 65 years of age and had a total score of 60 to 120 on the Positive and Negative Syndrome Scale (PANSS)⁽²⁰⁾. Those with other comorbid psychiatric disorders, clinically significant organic diseases, and a history of alcohol or drug abuse within the last 12 months were excluded. All patients were rated on the PANSS by psychiatrists trained in the use of this instrument and neuropsychological testing was administered by psychologists.

Prior to risperidone treatment, patients who were previously on typical neuroleptics went through a

Institute of
Mental Health
Woodbridge Hospital
10 Buangkok View
Singapore 539747

L Chua, BSc (Hons)
Senior Psychologist

S A Chong, MBBS,
MMed (Psych)
Associate Professor,
Consultant

E Pang, BA (Hons),
MSc (Clin Psych)
Senior Psychologist

V P Y Ng, BSc (Hons),
MPsych (Clin)
Psychologist

Clinical Trials &
Epidemiology
Research Unit
Ministry of Health
10 College Road
Singapore 169851

Y H Chan, PhD
Senior Medical
Statistician

Correspondence to:
Lyn Chua
Tel: (65) 389 2121
Fax: (65) 385 1052
Email: lyn_chua@
imh.com.sg

washout period (one week for oral medications and two weeks for depot medication). Upon starting risperidone, dosages were titrated in a stepwise manner until it reached a daily dose of 4 mg at Day 14. Thereafter, the dose was titrated according to the individual patient's clinical response. Anticholinergic agents were given only with the emergence of clinically significant extrapyramidal side-effects.

Baseline cognitive assessments were made before the washout period while patients were still receiving typical neuroleptics. They were reassessed 56 days (8 weeks) and 6 months after initiation of risperidone treatment. The cognitive tests included the Maze Test of the Wechsler Intelligence Scale for Children-Revised (WISC-R)⁽²¹⁾ which assesses executive function; Controlled Oral Word Association Test (COWA)⁽²²⁾ which assesses verbal fluency and retrieval from reference memory, and the Digit Symbol Test of the Wechsler Adult Intelligence Scale-Revised (WAIS-R)⁽²³⁾ which assesses perceptual/motor processing and attention. Tests of memory included the Logical Memory Passages (LMP) of the Wechsler Memory Scale (WMS)⁽²⁴⁾ - Immediate and Delayed Recalls for short and long-term verbal memory, the WMS Visual Reproduction for visual memory (immediate and delayed recalls) and the WAIS-R Digit Span test for immediate memory, attention span and concentration.

Scores for the WISC-R Maze test were obtained by converting the raw score (total number of points obtained on nine mazes) to a scaled score equivalent for age 16, which we modified for the adult population following Goldberg's methodology⁽²⁵⁾. For the measure of verbal fluency and retrieval from reference memory using the COWA, scores represented the total number of words starting with the letters "F, A and S" over a 60-second period and corrected for age and education⁽²²⁾. The local standardised versions of the Logical Memory Passages of the Wechsler Memory Scale were used; delayed recalls were made 45 minutes after presentation. Delayed recalls for the Visual Reproduction Tests were also made 45 minutes after presentation. Scores were calculated as instructed by the WMS Manual. For the Digit Span and Digit Symbol, raw scores were converted to a scaled score equivalent according to age as given in the WAIS-R Manual.

All the above tests (except two) were re-administered at 8 weeks and 6 months. These tests have been investigated for practice effects and shown not to have any significant influence on retesting⁽¹³⁾ except for the WMS Logical Memory Passages and Visual Reproduction. Forms II of these tests were used at 8 weeks. Changes in the PANSS and cognitive assessment test scores were evaluated by the Wilcoxon Signed Ranks Test.

Table I. Mean (SD) scores for cognition and psychopathology at baseline, 8 weeks and 6 months among the 12 patients.

Test	Baseline	8 weeks	p*	6 months	p*
Wechsler Memory Scale					
LMP (Immediate Recall)	5.4 (3.1)	7.2 (3.5)	0.052	7.0 (3.6)	0.075
Visual Reproduction (Immediate Recall)	6.5 (3.2)	10.9 (2.5)	0.003	9.8 (3.9)	0.025
Digit Symbol	6.9 (1.9)	7.8 (1.9)	0.093	7.6 (2.1)	0.255
COWA	25.7 (11.6)	30.3 (11.6)	0.005	28.9 (9.5)	0.123
Maze Test	5.2 (1.9)	6.4 (2.8)	0.227	6.8 (2.3)	0.036
Digit Span	7.5 (1.9)	7.5 (2.0)	1.000	8.1 (2.1)	0.196
Wechsler Memory Scale					
LMP (Delayed Recall)	3.6 (3.2)	6.1 (3.5)	0.045	6.0 (3.5)	0.029
Visual Reproduction (Delayed Recall)	4.3 (3.6)	7.8 (3.6)	0.012	9.2 (3.1)	0.003
PANSS Score					
Total	72.8 (10.3)	59.3 (11.8)	0.003	50.3 (9.3)	0.002
Positive	17.4 (3.6)	14.2 (4.5)	0.011	10.9 (2.9)	0.002
Negative	20.3 (5.7)	18.3 (5.3)	0.156	15.4 (4.1)	0.011
General	35.1 (5.4)	27.8 (6.2)	0.009	24.0 (4.1)	0.002

*p values are with reference to baseline

LMP = Logical Memory Passages; COWA = Controlled Oral Word Association

PANSS = Positive and Negative Syndrome Scale

RESULTS

Of the 12 patients (6 males and 6 females) who participated in the study, 8 were Chinese, 2 were Malays and 2 were Indians. The mean \pm SD age was 33.1 \pm 6.6 years (range 23 to 46) and mean \pm SD years of education was 9.9 \pm 2.1 years (range 7 to 13). The mean \pm SD duration of illness was 9.9 \pm 5.0 years (range 3 to 17). Total mean \pm SD PANSS score at baseline was 72.8 \pm 10.3 (range 63 to 97); at 8 weeks the mean \pm SD score was 59.3 \pm 11.8 (range 44 to 79) and at 6 months, the mean \pm SD was 50.3 \pm 9.3 (range 38 to 68).

While these patients were on typical neuroleptics, the mean daily dose of benzhexol was 3.2 mg/day. They were on 2.0 mg/day at 8 weeks of risperidone treatment and 2.2 mg/day at 6 months. The dosages of benzhexol were not significantly different at the three phases of assessment.

Table I shows the changes in PANSS scores and cognition at baseline, 8 weeks and 6 months. After 8 weeks of risperidone treatment, there was a significant reduction in the total PANSS score ($p=0.003$) with significant reductions in the positive and general subscales. Ratings at 6 months showed significant reductions on the total PANSS score ($p=0.002$) and on all the subscales.

Cognitive performance improved significantly on three measures of memory functioning after 8 weeks: delayed recall of Logical Memory Passages ($p=0.045$) and immediate and delayed recalls of Visual Reproduction ($p=0.003$ and $p=0.012$ respectively). Performance on COWA improved significantly at 8 weeks ($p=0.005$) but not at the 6-month follow-up. Improvements in the measures of memory functioning were sustained at the 6-month assessment: delayed recall of Logical Memory Passages ($p=0.029$) and immediate and delayed recalls of Visual Reproduction ($p=0.025$ and $p=0.003$ respectively), with significant improvements also in executive functioning (WISC-R Maze Test, $p=0.036$). There were improvements, although not statistically significant, in the performance of both digit symbol and digit span.

DISCUSSION

The results of the present study showed that risperidone brought about significant improvements in some cognitive functions in our patients with schizophrenia. Statistically significant improvements were found on measures of verbal and visual memory, and also in executive functioning. Verbal fluency improved significantly at 8 weeks but was not sustained at 6 months. While not statistically significant, there were improvements in measures of attention and perceptual/motor functioning.

Our findings are consistent with those of other studies which demonstrated that risperidone has positive effects on perceptual/motor processing, executive functioning, working memory, verbal learning and memory, motor function⁽²⁶⁻²⁷⁾.

Visual memory was significantly improved with risperidone in our study but Goldberg et al⁽²⁵⁾ found a significant decline in visual memory associated with clozapine treatment. Hagger et al⁽¹³⁾ found that improvement in negative symptoms while on clozapine treatment was associated with improvement in attention, executive function, verbal learning and memory, and verbal fluency. Similarly, with risperidone treatment, it is also likely that alleviation of negative symptoms is responsible for improvements in cognitive functioning.

There is still scanty data on the effects of the other atypical neuroleptics on the cognitive impairments associated with schizophrenia. A recent double-blind study which randomly assigned sixty-five patients to olanzapine (5-20 mg), risperidone (4-10 mg), and haloperidol (5-20 mg), reported that olanzapine has overall superior cognitive benefits relative to risperidone and haloperidol in the areas of motor skills, attention span, verbal and nonverbal fluency and reasoning, executive skills and immediate recall⁽²⁸⁾. However, the relatively small sample size limits the generalization of their findings. The authors also found improvements in verbal fluency and reasoning and immediate recall for risperidone which is consistent with our own findings.

One limitation of our study is the open-design with a small sample. We were unable in our study to establish the impact that the parallel improvement in psychopathology has on cognitive functioning. However, improvement in verbal working memory from risperidone treatment has been shown to occur independently of psychopathology⁽¹⁸⁾. Thus the overall clinical and cognitive response to risperidone treatment in the present study is similar to that observed in other studies. Our study is the first to report the impact of risperidone on cognitive functioning in Asian patients and, unlike previous reports, we followed up patients for a longer period with three assessments. Hagger et al⁽¹³⁾ reported that the major improvement in cognitive function was observed at six months amongst patients treated with clozapine. Sharma⁽²⁾ has argued that in order to evaluate the effects of drugs on cognitive function, the duration of treatment should be longer than six weeks, and preferably a year. Furthermore, he advocates that multiple assessments are necessary, with due attention to practice effects, in order to examine sustained improvement. However, the possibility that these improvements could be due to the wash-out of previous typical neuroleptics

cannot be resolved definitely except in a study design that examines neuroleptic-naïve first-episode schizophrenic patients and subsequently after typical and atypical neuroleptic treatment.

Several studies have demonstrated an association between poor social and occupational outcomes with these cognitive deficits^(9,29,30) which may be ameliorated by some of the atypical neuroleptics. Furthermore, the effect of improved cognitive skills on insight into illness may contribute to a positive mood state among patients with acute illness⁽²⁸⁾. These positive effects are likely to translate into more educational and vocational opportunities for patients with schizophrenia⁽²⁸⁾.

If atypical neuroleptics like risperidone are more effective in alleviating cognitive impairments in patients with schizophrenia, the high cost of these atypical agents can be justified as they will have a positive impact on the rehabilitation and quality of life of patients with schizophrenia. However, more head-to-head studies of the various atypical neuroleptics are required before any firm conclusion can be drawn with regards to their relative efficacy on the cognitive impairments of schizophrenia.

REFERENCES

- Gold JM, Harvey PD. Cognitive deficits in schizophrenia. *Psychiatric Clin Am* 1993; 16:195-312.
- Sharma T. Cognitive effects of conventional and atypical antipsychotics in schizophrenia. *Br J Psychiatry* 1999; 174 (suppl 38):44-51.
- Morice R. Cognitive inflexibility and prefrontal dysfunction in schizophrenia and mania. *Br J Psychiatry* 1990; 134:383-9.
- Kenny JT, Meltzer HY. Attention and higher cortical functions in schizophrenia. *J Neuropsych Clin Neurosci* 1991; 4:269-75.
- Braff DL, Heaton R, Kuck J, Cullum M, Moranville J, Grant I, Zisook S. The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. *Arch Gen Psychiatry* 1991; 48:891-8.
- Saykin AJ, Shtasel DL, Gur RE, Kestor DB, Moyley LH, Stafiniak P. Neuropsychological deficits in neuroleptic naïve patients with first-episode schizophrenia. *Arch Gen Psychiatry* 1994; 51:124-31.
- Lysaker PH, Bell MD, Bioty SM. Cognitive deficits in schizophrenia. Prediction of symptom change for participants in work rehabilitation. *J Nerv Ment Dis* 1995; 183(5):332-6.
- Meltzer HY, Thompson PA, Lee MA, Ranjan R. Neuropsychologic deficits in schizophrenia: relation to social function and effect of antipsychotic drug treatment. *Neuropsychopharmacology* 1996; 14 (3 Suppl):27S-33S.
- Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996; 153:321-30.
- King DJ. Psychomotor impairment and cognitive disturbances induced by neuroleptics. *Acta Psychiatr Scand* 1994; 380 (suppl 38):53-8.
- King DJ. The effect of neuroleptics cognitive and psychomotor function. *Br J Psychiatry* 1990; 157:799-811.
- Blider R M, Turkel E, Lipschutz Broch L, Reiter G, Geisler SH, Mayerhoff DI, et al. Antipsychotic medication effects on neuropsychological functions. *Psychopharmacol Bulletin* 1992; 28:353-66.
- Hagger C, Buckley P, Kenny JT. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biol Psychiatry* 1993; 34:702-12.
- Medallia A, Gold J and Merriam A. 1988. The effects of neuroleptics on neuroleptics on neuropsychological test results of schizophrenics. *Arch Clin Neuropsychol* 1988; 3:149-71.
- Borison RL. The role of cognition in the risk-benefit and safety analysis of antipsychotic medication. *Acta Psychiatr Scand* 1996; Suppl 389:5-11.
- Remington G. Understanding schizophrenia: the impact of novel antipsychotics. *Can J Psychiatry* 1995; 40(2 suppl):S29-32.
- Gallhofer, B, Bauer U, Lis S, Krieger S, Gruppe H. Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs. *Eur Neuropsychopharmacol* 1996; 6(suppl.2):S13-20.
- Green MF, Marshall BD, Wirshing WC, Ames D, Marder SR, McGurk S, et al. Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *Am J Psychiatry* 1997; 154:799-804.
- Chong SA, Yap HL, Low BL, Choo CH, Chan AOM, Wong KE, Mahendran R. Clinical evaluation of risperidone in Asian patients with schizophrenia in Singapore. *Singapore Med J* 1999; 40:41-3.
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizopr Bulletin* 1987; 13:261-76.
- Wechsler D. WISC-R Manual. Wechsler Intelligence Scale for Children-Revised, New York: Psychological Corp; 1974.
- Benton AL, Hamsher KdeS. Multilingual Aphasia Examination. Iowa City, Iowa: AJA Associates; 1989.
- Wechsler D. WAIS-R Manual. Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corp; 1981.
- Wechsler D and Stone LP. The Wechsler Memory Scale. New York: Psychological Corp; 1985.
- Goldberg TE, Greenberg RD, Griffin SJ, Gold JM, Kleinman JE, Pickar D, et al. The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia. *Br J Psychiatry* 1993; 162:43-8.
- Kern RS, Green MF, Marshall BD Jr, Wirshing WC, Wirshing D, McGurk SR. Risperidone versus haloperidol on secondary memory: can medications aid learning? *Schizophr Bulletin* 1999; 25(2):223-3.
- Meltzer HY, McGurk S. The effects of clozapine, risperidone and olanzapine on cognitive function in schizophrenia. *Schizophr Bulletin* 1999; 25:233-55.
- Purdon SE, Jones BDW, Stip E, Labelle A, Addington D, David SR, Breirer A, Tolleson GD for The Canadian Collaborative Group for Research on Cognition in Schizophrenia. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. *Arch Gen Psychiatry* 2000; 57:249-58.
- Brekke JS, Raine A, Ansel M, Lencz T, Bird L. Neurological and psychological correlates of psychosocial functioning in schizophrenia. *Schizophr Bulletin* 1997; 23:19-28.
- Jaeger J, Douglas E. Neuropsychiatric rehabilitation for persistent mental illness. *Psychiatr Q* 1992; 63:71-94.