Clinical Evaluation of Risperidone in Asian Patients with Schizophrenia in Singapore

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ABSTRACT

Objective: To evaluate the short-term efficacy and safety of risperidone in a group of Asian patients with schizophrenia in an 8-week open-label, prospective study.

Methods: Patients with DSM-IV schizophrenia were recruited from Woodbridge Hospital. After a washout period, they were started on a 56-day trial of risperidone. Outcome was assessed with the positive and negative syndrome scale (PANSS), the clinical global impression scale (CGI) and the extrapyramidal symptom rating scale (ESRS).

Results: The mean daily risperidone dose at end point was 5.6 mg (range, 3 to 8 mg/day). Mean PANSS scores were reduced significantly from 78 ± 15.1 at baseline to 56.6 ± 10.9 at end point. Seventeen patients (85%) who were treatment responders, showed at least a 20% reduction in total PANSS scores at end point while nine patients (45%) had a greater than 50% reduction in the total PANSS scores. According to the CGI scale, 85% improved at end point. The severity of extrapyramidal symptoms (mean ESRS scores) were significantly lower at end point than at baseline.

Conclusions: Risperidone was effective in the treatment of positive and negative symptoms of schizophrenia.

Keywords: treatment of schizophrenia, Asian patients, risperidone, extrapyramidal symptoms

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INTRODUCTION

Singapore is among the first few countries in South East Asia to use risperidone for the treatment of schizophrenia. In two large, multicenter, double-blind, controlled, comparative studies[1-3] in the West, risperidone at doses of 6 to 8 mg was shown to be effective in ameliorating the positive and negative symptoms of chronic schizophrenia and to be well tolerated. The severity of extrapyramidal symptoms (EPS) in patients treated with risperidone was significantly lower than in patients receiving haloperidol and not significantly higher than with placebo.

The aim of the present study was to evaluate the short-term efficacy and safety of risperidone in a group of Asian patients with schizophrenia who were treated at Woodbridge Hospital in Singapore.

METHOD

Patients who met the DSM-III-R[4] criteria for schizophrenia, were recruited from Woodbridge Hospital, a state psychiatric institution in Singapore. Each patient or the patient's legal guardian gave written informed consent to participate in the study. The study was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki (1964) revised in Tokyo (1975), and the subsequent Venice (1983) and Hong Kong (1989) amendments.

Selected 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)[5]. Excluded were pregnant or lactating women or sexually active women without adequate contraception, as well as patients with a mental disorder other than schizophrenia or with significant physical illness or a history of substance or alcohol abuse.

The study was an 8-week, open-label trial. The primary measure of efficacy was defined as a 20% or greater reduction in the baseline total PANSS score at end point. Psychopathology was also assessed by means of the clinical global impression improvement scale[6]. Severity of EPS was assessed with the extrapyramidal symptom rating scale (ESRS)[7]. The investigators were trained in the rating of the PANSS and ESRS with the help of videotapes of patient interviews that were produced by the authors of the scales.

Before commencing on risperidone, all the patients underwent a 1-week washout period of oral medications. Patients receiving depot antipsychotics were started on risperidone at the midpoint of the week that they would have received their next injection. Antiparkinsonian medications were continued during the washout period; however, they were adjusted or stopped during the trial, depending on each patient's symptoms.

The risperidone dose was titrated, up to a daily dose of 4 mg at day 14, and thereafter adjusted according to the patient's clinical response.

Symptoms were rated at baseline and at 1, 2, 4, 6, and 8 weeks of risperidone treatment. Haematological and blood chemistry (urea/electrolytes, serum creatinine, and liver enzymes) tests were performed at baseline and at study end point. Other adverse

reactions were evaluated by patient query and observation by the study psychiatrists.

Measured values are expressed as means ± SD (standard deviation). Characteristics and clinical ratings were compared using Wilcoxon's signed rank test.

RESULTS

Of the 20 patients who completed the 8-week trial, 16 were Chinese, 2 were Malays, and 2 were Indians (Table I). The schizophrenia subtypes included disorganised (7 patients), undifferentiated (5 patients), paranoid (6 patients), and residual (2 patients). The patients' mean age was 34.8 ± 8.8 years (range, 19 to 53). The mean duration of illness was 10.6 ± 7.3 years (range, 2 to 30), with a mean age of onset at 24.3 ± 7.6 years (range, 11 to 45). Fourteen patients had been receiving depot medication prior to the study. The mean end point risperidone dose was 5.6 mg/day (range, 3 to 8 mg/day).

Efficacy

Symptoms of psychopathology were significantly ameliorated during the trial: PANSS total scores were reduced from a mean of 78 ± 15.1 at baseline to 56.6 ± 10.9 at end point (p < 0.01) (Table I). Seventeen (85%) of the 20 patients were treatment responders (exhibited a 20% or greater reduction in total PANSS score at end point). Nine patients (45%) exhibited a 50% or greater reduction in total PANSS score. No differences were found between treatment responders and non-responders in age, age of illness onset, illness duration, baseline total scores of the PANSS and ESRS, and the mean daily dose of risperidone.

Reductions in scores from baseline to end point were noted in all but 1 of the 30 individual PANSS items (mannerisms and posturing: 1.0 at baseline, 1.2 at end point; not significant). Items that showed a significant reduction are shown in Table II; they include 4 of the 7 positive symptoms, 4 of the 7 negative symptoms, and 6 of the 16 symptoms of general psychopathology.

Clinical global impression scores indicated that 17 (85%) out of 20 patients improved at end point: 2 (10%) were very much improved, 10 (50%) much improved, and 5 (25%) minimally improved, and 3 (15%) were unchanged.

Extrapyramidal symptoms

Severity of EPS was significantly reduced during treatment: mean total ESRS scores were 9.4 ± 9.3 at baseline and 5.4 ± 3.2 at end point (p < 0.05) (Table I). ESRS scores were reduced in 12 out of 20 patients, were unchanged in 3, and increased in 5.

Sixteen out of 20 patients were receiving anti-parkinsonian medication (trihexyphenidyl) before the trial, compared with 12 patients at end point. Although the mean dose of trihexyphenidyl was lower at the end of the trial (2.5 ± 2.7 mg/day versus 3.8 ± 2.4 mg/day at baseline), the reduction was not statistically significant.

Other adverse events

Other adverse events reported include giddiness in three patients, headache in two, and agitation in another two patients. One female patient reported galactorrhea and another developed obsessive-compulsive symptoms. No haematological abnormalities were detected at the end of the trial.

Table I – Patient characteristics, responses to treatment, and severity of extrapyramidal symptoms

Patient	Sex/ Ethnicity	Age (yr)	Age of onset (yr)	Duration of illness (yr)	Weight (kg)	Final dose (mg)	PANSS total baseline	% PANSS reduction	ESRS total baseline/ end point
1	M/C	34	28	6	63	5	63	58	4/2
2	F/C	26	16	10	44	2	91	85	32/4
3	M/C	23	20	3	44	4	74	64	4/4
4	F/C	43	24	19	81	6	62	59	7/8
5	F/C	45	28	17	51	6	66	61	4/8
6	M/C	33	18	15	84	4	93	54	0/4
7	F/C	43	27	16	53	8	92	36	32/11
8	F/M	33	26	7	66	6	63	39	3/3
9	M/C	19	16	3	54	8	114	69	1/0
10	F/C	32	30	2	66	6	102	51	1/7
11	F/C	53	23	30	62	6	88	59	9/9
12	M/C	30	25	5	89	4	72	40	6/3
13	F/I	46	36	10	58	4	68	21	4/6
14	M/C	31	16	15	68	6	90	18*	18/7
15	F/C	47	45	2	47	3	77	23	6/1
16	M/C	37	23	14	70	6	63	18*	16/10
17	F/C	30	27	3	62	6	65	29	11/4
18	M/C	28	11	17	75	7	63	33	6/2
19	M/C	32	24	8	76	4	81	12*	17/9
20	F/I	31	22	9	77	8	74	25	6/5

PANSS = Positive and Negative Syndrome Scale, ESRS = Extrapyramidal Symptom Severity Scale
C = Chinese; M = Malay; I = Indian
* Non-responder to treatment

Table II – PANSS individual items whose mean (±SD) scores were reduced significantly

Item		Baseline	End Point
P1	Delusions	3.6 ± 2.1	2.4 ± 1.6*
P2	Conceptual disorganisation	3.3 ± 1.7	1.9 ± 1.0**
P3	Hallucinatory behaviour	4.6 ± 2.2	2.8 ± 1.8***
P7	Hostility	2.0 ± 1.3	1.2 ± 0.6*
N2	Emotional withdrawal	3.3 ± 1.2	2.5 ± 1.0**
N3	Poor rapport	2.7 ± 1.3	2.0 ± 0.8*
N4	Passive/apathetic social withdrawal	3.8 ± 1.5	2.8 ± 1.2**
N5	Difficulty in abstract thinking	4.0 ± 2.9	2.9 ± 1.0**
G2	Anxiety	2.4 ± 1.2	1.7 ± 0.9*
G9	Unusual thought content	3.0 ± 1.8	1.6 ± 1.1**
G12	Lack of judgement and insight	4.2 ± 1.2	3.3 ± 1.2**
G13	Disturbance of volition	3.4 ± 1.5	2.4 ± 1.0*
G15	Preoccupation	3.2 ± 1.8	1.8 ± 0.9**
G16	Active social avoidance	3.2 ± 2.5	2.5 ± 1.2*

P = positive symptoms   N = negative symptoms   G = general psychopathology

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

CONCLUSIONS

The 85% response rate of the patients in the present study is greater than that found in the North American trial (61% at a fixed dose of 6 mg/day of risperidone)[1,2] or in the multinational study (63% at 4 mg/day and 66% at 8 mg/day of risperidone)[3]. In these studies, there is good agreement that the daily risperidone dose of 4 to 8 mg is optimal. The mean dose of our responders (5.6 mg/day) fell within this range.

An 8-week trial may be insufficient to gauge response to an antipsychotic agent in schizophrenia since the efficacy of the drug may not be manifested for 3 to 4 weeks after each dose adjustment[8]. A long-term study of risperidone-treated patients found further significant reductions in symptoms of schizophrenia by 1 and 2 years[9]. Thus it can be expected that more of the patients may improve with continued treatment.

Although the total mean ESRS score was significantly lower at end point than at baseline, 60% (12 of 20) still required antiparkinsonian medication. Because the washout period was rather short and most of the patients were receiving depot antipsychotic treatment before the trial, residual antipsychotic effects may have contributed to increased EPS and possibly made the patients more sensitive to EPS. Another factor may be ethnic differences. Asian patients have been shown to be more sensitive to haloperidol-induced EPS[10]. It has been suggested that Asians are more sensitive to the dopaminergic blockade of antipsychotics and may require low doses of risperidone[11].

The role of risperidone in treatment-refractory schizophrenia is yet to be established. The characteristics of our sample – mean age of 34 years, duration of illness more than 10 years, and 7 prior hospitalisations – suggest that many poor or partial responders to conventional antipsychotics were included in the study. This suggests that risperidone may be effective in treatment-refractory schizophrenia.

The study has a number of limitations, including the small sample size, the lack of a placebo and active drug control group, and the open design that could have inflated the response rate. The clinical status of the patients also did not permit an adequate period of washout for those who had been on depot antipsychotics. Nonetheless, the findings suggest that risperidone is effective and well tolerated in Asian patients with schizophrenia.

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