Indian Journal of Psychiatry, 2001, 43 (2),152-156

AN OPEN CLINICAL TRIAL WITH RISPERIDONE IN CHRONIC SCHIZOPHRENIA

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ABSTRACT

Recent clincial experience with risperidone indicates that it has a broad spectrum of antipsychotic activity, alleviating positive and negative symptoms as well as mood symptoms in schizophrenia, and a better side effect profile as compared with conventional antipsychotics. The purpose of the present study was to evaluate the efficacy of risperidone in chronic schizophrenia but more especially to estimate the neurological side effect profile in Indian setting. In an open clinical trial, 24 DSM-IV chronic schizophrenic patients received risperidone monotherapy for 12 weeks. Clinical assessments, utilized the Positive and Negative Syndrome Scale for Schizophrenia, the Simpson - Angus Extrapyramidal Symptoms Rating Scale, and the Clinical Global Impression Scale. All the patients showed significant improvement in positive, negative and depressive symptoms at every follow up, relative to the baseline scores. One-fourth of the sample experienced mild to moderate extrapyramidal side effects, such as tremor (35%), salivation (25%), rigidity (65%), gait disturbance (30%), and akathisia (15%). Two patients dropped out at 8 weeks because of no improvement, and two patients dropped out at 10 weeks due to intractable akathisia. The high prevalence of extrapyramidal side effect was unexpected.

Key words : Risperidone, schizophrenia, positive symptoms, negative symptoms, extrapyramidal symptoms

Risperidone, a benzisoxazole derivative with selective balanced antagonism of serotonin $5HT_2$ receptors and dopamine D_2 receptors. Unwanted dopaminergic blockade in the nigrostriatal tract is partially overcome through blockade of serotonergic receptors, thereby lessening extrapyramidal symptoms. Potent dopaminergic blockade in the mesolimbic area attenuates positive symptoms. Hypodopaminergia in the prefrontal cortex, which underlies negative symptoms, responds to a net increase in dopaminergic activity as a result of D_2 - $5HT_2$ receptor antagonism (Lysen et al.,1994). In addition, the possible thymoleptic action associated with serotonin $5HT_2$ receptor antagonism may be of value in psychotic patients with prominent affective symptoms (Keck Jr. et al.,1996). Recent studies have reported risperidone to be a broad spectrum antipsychotic agent, effective for both positive and negative symptoms of schizophrenia (Marder and Meibach,1994). Risperidone may also carry a lower risk of extrapyramidal symptoms and tardive dyskinesia (Owens,1996). Recently, however, reports of risperidone - induced extrapyramidal side effects have appeared, namely dystonic reaction, akathisia and tardive dyskinesia, from India and the West (Buzan,1996; Faulk et al.,1996) and one study showed comparable rates in incidence and severity of extrapyramidal syndromes with that of haloperidol (Rosebush and Mazurek, 1999). Thus the present study was undertaken to evaluate the efficacy of risperidone as well as its extrapyramidal side effects in an open trial in chronic schizophrenics in an Indian

setting.

MATERIAL AND METHOD

Patients with DSM-IV chronic schizophrenia with or without acute exacerbation were selected. Informed consent was obtained from all patients. Detailed physical examination was done to rule out concurent chronic medical illness, and haematological screening to rule out diabetes, hepatic and renal damage. No patient was receiving depot neuroleptics. Patients on oral neuroleptics underwent a 1 week drug washout. Risperidone was initiated at a dose of 2 mg/day, which was increased to a maximum daily dose of 8 mg/day by an increment of 2 mg every 3 to 4 days over a period of 4 weeks, depending on the improvement and the presence of side effects. The permitted concomitent medications were trihexiphenidyl, propranol and benzodiazepines.

Patients were rated using the Positive and Negative Syndrome Scale for Schizophrenics (PANSS; Key et al.,1987). The PANSS was administered at baseline and every 2 weeks till the completion of study. Overall efficacy was assessed using the Clinical Global Impression Scale (CGI) at baseline, and at 4, 8 and 12 weeks. The occurence of extrapyramidal side effects was assessed using the Simpson Angus Extrapyramidal Rating Scale (1970) at weeks 1, 4, 8 and 12. Ratings at different time points up were compared with baseline scores using Wilcoxon Matched - Paired Signed - Rank test with Bonferroni correction for multiple comparisons.

RESULTS

A total of 24 patients aged 15 to 56 years (mean 35.58±11.18, median 37) were included in this study. There were 20 males and 4 females. The mean duration of illness was 8.96±5.13 years (range 2-24 years). The mean daily dose of risperidone was 7.17±1.01 mg (median 8). Out of 24 patients, 12 received trihexphenidyl, 6 received benzodiazepines, and 4 had received propranol at various points of time during the course of treatment. Two patients dropped out at 8 weeks due to poor response, and an additional 2 patients dropped out at 10 weeks due to intractable akathisia.

Comparison of the mean rank score of the positive syndrome subscale at baseline with values at 2, 4, 8, 10 and 12 weeks showed statistically significant reductions at each point time. Similarly, the mean rank score of the negative syndrome subscale, general psychopathology subscale and depression subscale showed significant reductions compared with baseline score at all points time. Clinical Global Impression (CGI) mean rank score was significantly reduced at 4, 8 and

TABLE 1

PANSS AND CGI SCORES AT DIFERENT TIME POINTS

PANSS subscale	Base line (n=24)	Week2 (n=24)	Week4 (n=24)	Week6 (n=24)	Week8 (n=22)	Week10 (n=20)	Week12 (n=20)
		***	***	***	***	***	***
Positive symptom	22.5 ±7.5	17.04 ±5.40 ***	12.92 ±5.47 ***	10.88 ±4.82 ***	9.91 ±4.22 ***	9.55 ±4.19 ***	9.22 ±3.86 ***
Negative symptom	28.75 ±5.90	24.17 ±7.78 ***	19.43 ±6.81 ***	15.96 ±5.89 ***	15.00 ±4.85 ***	2.90 ±5.55 ***	12.10 ±5.50 ***
General psychopathology	50.42 ±9.67	43.17 ±11.61 ***	37.17 ±9.87 ***	31.50 ±6.88 ***	29.00 ±6.19 ***	26.50 ±7.71 ***	25.50 ±6.87 ***
Depression	10.60 ±5.11	8.96 ±4.22	8.36 ±3.90	7.16 ±3.67	6.50 ±3.35 ***	5.95 ±3.03	5.90 ±3.91 ***
CGI	4.52 ±1.14		2.64 ±0.184		2.26 ±0.134		2.00 ±0.122

** p<0.01 *** p<0.001, compare with baseline
(Data are mean±standard deviation)

TABLE 2
PREVALENCE OF EXTRAPYRAMIDAL SIDE EFFECTS

	Week1		Week4		Week8		Week12	
	No.	%	No.	%	No.	%	No.	%
Tremor	4	16.7	7	29.2	7	31.9	7	35.0
Salivation	6	25.0	9	37.5	6	27.3	5	25.0
Rigidity	10	41.7	15	62.5	13	59.1	13	65.0
Gait disturbance	6	25.0	7	29.2	7	31.9	6	30.0
Dystonia	2	8.3	2	8.3	0	0.0	0	0.0
Akathisia	4	16.7	4	16.7	3	13.7	3	15.0

12 weeks as compared to.the baseline (Table 1). Prevalence of moderate to severe extrapyramidal side effects (Simpson - Angus symptom item score more than 2) was 50% at the end of trial. The extrapyramidal side effect profile (Table 2) showed that the most frequently observed side effect was rigidity followed by tremor, gait disturbances, salivation, akathisia and dystonia.

DISCUSSION

Risperidone was effective against both positive and negative symptoms at doses ranging from 6-8 mg/day. This in agreement with previous reports of a broad spectrum of antipsychotic effect (Marder and Meibach,1994; Agashe et al.,1994; Agarwal et al.,1998). A meta-analysis of pooled results from six double blind trials showed that risperidone (4 to 8 mg/day) had a significantly higher negative symptoms response rate, defined as the percentage of patients with a 20% or more reduction in scores on the negative subscale of PANSS, than patients receiving drugs such as haloperidol, perphenazine or zuclopenthixol (Carman et al.,1995). Improvement in negative symptoms with risperidone may be due to change from a net hypodopaminergic activity in prefrontal cortex to a net resultant in increased dopaminergic activity as a result of balanced D_2 -$5HT_2$ antagonism (Kapur and Remington,1996). In this study, risperidone was also found to be effective against depressive symptoms in schizophrenia, showing that mood symptoms are amenable to treatment. Azorin (1995) in a study of long - term treatment of mood disorders in schizophrenia showed that risperidone is more effective than haloperidol in patients with high anxiety/depression scores. Thus, risperidone appeares to be a good candidate for the long term treatment of mood disturbance in schizophrenia, although long-term, double blind, controlled studies are needed to confirm this.

Many patients in this series experienced extrapyramidal side effects. The commonest side effect observed was rigidity followed by tremor, salivation, gait disturbances and akathisia. Literature emphasizes the benign extrapyramidal side effect profile of risperidone at therapeutic doses (Marder and Meibach,1994). However, Carman (1993) reported a modest increase in extrapyramidal side effect ratings of bradykinesia, global dyskinesia and parkinsonism in a one year trial of risperidone at doses of 6-16 mg/day. There are case reports of acute dystonia (Faulk et al.,1996) and akathisia associated with risperidone initiation. Hoyberg et al. (1993), in a randomised trial of risperidone (mean dose 8.5 mg/day) versus perphenazine (mean dose 28 mg day), found no difference in the extrapyramidal side effects between these two drugs or in the use of antiparkinson drugs. Agarwal et al. (1999), in an open trial of risperidone (mean dose not specified) in Indian patients, found a prevalence rate of 39.4% extrapyramidal side effects when clubbing tremor (39.4%), rigidity (18%), bradykinesia (29%) and akathisia (14%) at the end of study. These rates are comparable with the rates reported in the present study except high rate of rigidity in the index series. The number of patients who were started antiparkinsonian medications (50%) indicates the severity of extrapyramidal side effects, which needed active intervention. Agashe et al. (1999) in a trial of risperidone (mean dose not specified) in

30 Indian patients with schizophrenia reported a prevalence rate of 40% adverse events when clubbing tremor (13.33%) rigidity (10%), salivation (10%), oculogyric crisis (3.33%) and akathisia (3.33%). Saxena et al. (1996), in a trial of risperidone augmentation of fluoxetine for refractory obsessive - compulsive disorder, found that 24% of patients experienced side effects (most commonly akathisia) which forced discontinuation of medication. In the present study 17% had intractable akathisia, which neccessitated discontinuation of risperidone. The prevalence of extrapyramidal side effects in this study was almost comparable to any classical antipsychotics. Recently Rosebush and Mazurek (1999) compared the side effect profile of risperidone (mean dose, 3.2 mg/day) with that of haloperidol (mean dose, 3.7 mg/day) in neuroleptic naive patients. Prophylatic anticholinergic medications were not routinely used. They found that all extrapyramidal syndromes were comparable in incidence and severity in the two groups. Recently, sporadic report are available about tardive dyskinesia with risperidone after long - term treatment (Buzan, 1996; Woener et al.,1996).

These data suggest that previous literature not withstanding, extrapyramidal side effects are common with risperidone. Clinical trials with risperidone have shown a unique therapeutic window in the effect of producing extrapyramidal symptoms (Kapur and Ramington,1996). At a dose of 6 mg/day, risperidone demonstrates higher $5HT_2$ (80-100%) than D_2 (74-83%) occupancy bordering on the extrapyramidal threshold. At this dose, the presence of potent $5HT_2$ antagonism may reduce risperidones risk of EPS in comparison with conventional antipsychotics. As the dose of risperidone is increased beyond 6 mg/day suprathreshold D_2 blockade may result and the balanced serotonin dopamine interaction may no longer be able to alleviate extrapyramidal symptoms. In the present study, the mean dose of risperidone was 7 mg/day which was above the threshold of balanced $5HT_2$ dopamine D_2 antagonism thereby producing EPS. Another possibility to be considered is the racial changes in the pharmacokinetic and pharmacodynamic profile of risperidone making Indian patients more susceptable to extrapyramidal side effects. Asian patients appear to require lower doses of most psychotropic medications than do Caucasian patients (Jeste et al.,1996). This may explain why certain patients in India respond to risperidone at doses that are as low as 1 mg/day.

This being an open, uncontrolled trial, there remains the possibility of bias in the rating of psychopathology as well as the neurological side effect profile. Neverthless, this study suggests that risperidone has a primary role in the treatment of schizophrenia, alleviating positive and negative symptoms as well as depressive symptoms. However, extrapyramidal side effects may be commoner than earlier believed.

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