

RISPERIDONE IN SCHIZOPHRENIA

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ABSTRACT

Efficacy and safety of new antipsychotic agent-risperidone was evaluated in the confirmed schizophrenic patients of either sex, over 15 years of age. Of the 30 patients who entered the study, 27 completed the trial as per the protocol and only 3 dropped out, one was lost to follow up, the other was an uncooperative patient who pulled out of the trial due to moderate side effects while one patients withdrew the consent at his own free will. The significant improvements were seen in the broad range of symptoms of schizophrenia at various time points in the trial. The significant beneficial effect on negative symptoms was particularly obvious. The drug was well tolerated by most patients, and side effects, when reported, were mild. Even the extrapyramidal symptoms reported could be easily controlled with oral trihexyphenidyl hydrochloride. The exhaustive extrapyramidal symptom rating scale also did not show any worsening during risperidone therapy. The efficacy and safety profile of novel antipsychotic drug risperidone makes it a useful therapeutic agent in the broad range of patients with schizophrenia.

Key Words : Schizophrenia, risperidone, new antipsychotic agent, therapeutic efficacy, therapeutic safety

The well established effectiveness of currently available antipsychotic agent is offset by their limitations. These agents are not useful in all psychotic patients, and many a times they cause serious neurological side effects. At times, even the patients responding to them are left with serious disabilities. Such limitations have made psychiatrists to look for agents with better or at least similar efficacy and with lesser side effects causing potential.

Risperidone is a novel antipsychotic agent which combines potent serotonin 5HT₂ and dopamine D₂ receptor antagonism (Grant & Kitton, 1994). Advantages offered by risperidone over haloperidol include a faster onset of antipsychotic action, a lower incidence of extrapyramidal effects and greater efficacy against the negative symptoms of schizophrenia. It is suggested that risperidone may also

play a role in reducing hospital days for the chronic schizophrenic population (Addington et al., 1993).

At our centre we have substantial number of patients who have a long standing history of schizophrenia and they are either not adequately controlled with the existing neuroleptics or develop side effects with them. We decided to evaluate the broad spectrum antipsychotic agent-risperidone in our schizophrenic patients to assess its safety and efficacy. The effort was also made to evaluate the effect of risperidone on negative symptoms and to assess whether the beneficial effects were achievable without increasing the occurrence of side effects.

MATERIAL & METHOD

The open study with a treatment duration of 4 months was designed.

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The frequency and timings of various safety evaluations are represented in the following table

	VISIT	1	2	3	4	5	6	7	8	9	10
	DAY	0	7	14	28	6	8	10	12	14	16
	WEEKS										
Physical exam. & weight		X									X
Lab., ECG		X									X
Vital signs		X	X	X	X	X	X	X	X	X	X
PANSS & BPRS		X			X			X			X
CGI		X	X	X	X	X	X	X	X	X	X
ESRS		X			X			X			X
Adv. Exp.			X	X	X	X	X	X	X	X	X
Disp. Med.		X	X	X	X	X	X	X	X	X	

Patients inclusion criteria : Patients of either sex, over the age of 15 years and diagnosed as suffering from schizophrenia or schizophreniform disorder (as per DSM-III-R criteria) were considered for the study.

The patients with any of the following were excluded from the study :

- Women in reproductive age group without adequate contraception.
- Pregnancy and lactation.
- Patients receiving a depot neuroleptic within one treatment cycle of the time of selection.
- Patients receiving oral/parenteral neuroleptic within 3 days prior to the day of selection for study.
- Patients with clinically relevant organic/neurologic disease or abnormal laboratory tests, or with abnormal ECG findings.
- Patients with a diagnosis of psychoactive substance abuse.
- Patients who were included in trial with investigational drugs during the 4 weeks preceding this trial.

During the first week of the trial, the patients were preferably hospitalised, if possible. Thereafter, they were treated on an in or out patient basis.

Before entering the study an informed, written consent was obtained from each of the patient.

Each patient received risperidone 1 mg

twice a day on day one, 2 mg twice a day on day two, and 3 mg twice a day on day three. The dosage of 3 mg twice a day was continued till the end of first week. On 7th day, if the Clinical Global Impression (CGI) was rated as "improved" then that patient's total daily dose (6 mg) remained unchanged. If on day 7, CGI was rated as "unchanged" or "worsened" then the total daily dose was increased to 8 mg (4 mg twice a day). On day 14, the same previous daily dose was continued if CGI rating was improved. If the rating was "unchanged" or "worsened" the daily dose of risperidone was increased by 4 mg per week without exceeding the maximum daily dose of 16 mg. (2 tablets of 4 mg. twice a day). From day 29 onwards for the next 3 months the dose of risperidone was kept unchanged as far as possible. However, dose adaptations were permissible if necessary.

During the trial period, except for risperidone, no other antipsychotic was administered. All other concomitant medications received by the patients were recorded in detail. Any patient developing extrapyramidal symptoms was prescribed an anticholinergic, if necessary. Benzodiazepine was used, only when required, for additional sedation.

Efficacy evaluation :

Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1992) for schizophrenia

and Brief Psychiatric Rating Scale (BPRS) were used. Overall efficacy was assessed using the Clinical Global Impression (CGI). The frequency and timings of these evaluations are represented in the following table.

Safety evaluation

To achieve this the following criteria were used.

(a) Routine physical & neurological examination

(b) Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard *et al.*, 1980)

(c) Vital signs

(d) Laboratory tests

-Haematology : hemoglobin, RBC count, WBC count (total & differential), platelet count.

-Blood biochemistry : sodium, potassium, chloride, total protein, glucose, total bilirubin, alkaline phosphatase, GGT, AST, ALT, urea, creatinine, uric acid.

-Urine analysis : protein, glucose, occult blood.

-ECG

All the cases, throughout the trial were closely monitored for any adverse effects. When noted, adverse effects were recorded in detail. The authors used Wilcoxon matched-pairs

TABLE 1
PANSS, BPRS & CGI (MEAN SCORES)

	Basal (± S.E.)	Week 4 (± S.E.)	Week 10 (± S.E.)	Week 16 (± S.E.)
Positive	15.04 (1.067)	12.63*** (0.766)	11.11*** (0.902)	10.78*** (0.909)
Negative	21.56 (1.326)	18.89** (1.079)	16.70*** (0.929)	16.11*** (1.162)
General	35.74 (1.249)	31.67*** (1.425)	28.44*** (1.385)	27.44*** (1.442)
Total PANSS	72.33 (2.837)	62.82*** (2.384)	56.26*** (2.576)	54.33*** (2.990)
BPRS	38.96 (1.897)	33.82*** (1.444)	30.44*** (1.328)	29.07*** (1.377)
CGI	3.52 (0.135)	3.00** (0.131)	2.52*** (0.154)	2.26*** (0.156)

*p<0.05. **p<0.01. ***p<0.001

TABLE 2
EXTRAPYRAMIDAL SYMPTOMS RATING SCALE (ESRS)

ESRS	Mean Scores			
	Basal (± S.E.)	Week 4 (± S.E.)	Week 10 (± S.E.)	Week 16 (± S.E.)
Questionnaire total score	0.926 (0.244)	0.704 (0.198)	0.667 (0.220)	0.630 (0.201)
Parkinsonism total score	1.889 (0.493)	1.852 (0.626)	2.074 (0.823)	1.85 (0.472)
Dystonia total score	0.000 (0.000)	0.000 (0.000)	0.037 (0.037)	0.000 (0.000)
Parkinsonism + Dystonia total score	1.889 (0.493)	1.852 (0.626)	2.111 (0.824)	1.185 (0.472)
Dyskinesia total score	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
Parkinsonism + dyskinesia total score	1.889 (0.493)	1.852 (0.626)	2.111 (0.824)	1.185 (0.472)
Clinical Global Impression (CGI) of dyskinesia	0.222 (0.154)	0.148 (0.116)	0.037 (0.037)	0.000 (0.000)
Clinical Global Impression (CGI) of parkinsonism	0.630 (0.178)	0.704 (0.212)	0.778 (0.252)	0.667 (0.192)

signed-ranks test for the statistical analysis of efficacy and the safety results wherever applicable.

RESULTS

The study was conducted at Maharashtra Institute of Mental Health, Mental Health Promotion, Training and Research Organisation, Sassoon Hospital Campus, Pune, from February, 1996 to June, 1997.

A total of 30 cases (28 males and 2 females) were enrolled in the trial. The mean age of the patients was 30.9 years while median age was 28.5 years. The mean duration of schizophrenic disease in our patient population was 6.92 years (minimum 1 year/ maximum 25 years). The majority of the

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TABLE 3
ADVERSE EVENTS

	No. (%) of patients
Tremor	4 (13.33)
Rigidity	3 (10.0)
Sialorrhoea	3 (10.0)
Extrapyramidal symptoms	1(3.33)
Nausea and vomiting	1(3.33)
Headache	1(3.33)
Pain in abdomen	1(3.33)
Palpitation	1(3.33)
Oculogyric crisis	1(3.33)
Akathisia	1(3.33)

patients (26 out of 30) were less than 45 years of age.

Three of the patients dropped out of the study. One was lost to follow up, the other patient was uncooperative and complained of insufficient response, and dropped out of the trial as he also had adverse effects (headache, pain in abdomen and palpitations). One patient withdrew the consent for the trial at his own free will. The remaining 27 patients completed the trial as per the protocol. The analysis has been carried out of the complete data available from 27 patients, however, the side effects occurrence covers all the 30 patients. Statistical analysis indicated that there were no significant differences in the baseline readings (age, PANSS and sub scales, BPRS) between the patients completing the trials and the ones that dropped out.

There were consistent and highly significant reductions in the mean scores attributed to the positive, negative and the general psychopathological symptoms as well as total PANSS scores at all the time periods (4, 10 and 16 weeks). The improvements were noted earlier in many patients. Highly significant reductions were also noted in mean BPRS scores at

4, 10 as well as 16 week (Table 1). Eighteen patients (66.7%) had reduction of 20% or more in their total PANSS scores at the end of 16 weeks and hence were considered clinically improved. Seventeen patients (62.9%) showed similar reduction in their BPRS scores.

Clinical Global Impression (CGI) mean scores also were significantly reduced at 4, 10 and 16 weeks as compared to the baseline (Table 1). At 16 weeks eighteen patients (66.7%) were considered as not ill, or mildly so. Seventeen patients (63.0%) were considered as very much or much improved as compared to their condition at the start of the trial.

The exhaustive Extrapyramidal Symptom Rating Scale (ESRS) mean scores revealed that there were no significant differences in any of the parameters studied (Table 2) as compared to the baseline status at all the time points in the study (4, 10 and 16 weeks).

Adverse events reported have been listed in table 3. The one or more adverse events were reported by 12 (40%) patients, however, they were mild and did not necessitate the discontinuation of therapy except in one case. The Extrapyramidal Symptoms (EPS), were mild, and treated with trihexyphenidyl hydrochloride tablets.

One of the patients continued to complain of nausea and vomiting and hence the dose was reduced to 4 mg and maintained at that level throughout. The other patient when given 8 mg developed tremors, the reduction of risperidone dose to 4 mg a day and administration of trihexyphenidyl hydrochloride tablets completely controlled the adverse effects and he was then maintained at that dose. The mean daily dose of risperidone used was 8.96 mg in our patients who had a long standing history of schizophrenia.

The mean weight showed a rise at the end (65.7 kg) of trial as compared to the pretherapy (63.9 kg) level.

DISCUSSION

Risperidone was significantly effective in

causing the improvements in most of the schizophrenic patients enrolled in the study. Most of the patients tolerated the effective recommended doses. The improvements were seen in positive as well as general psychopathological symptoms, as indicated by the scores. The very impressive fact was that there were marked improvements in the negative symptoms as well. The improvements also tended to occur speedily.

The ability of risperidone to continue to be effective and safe even on long term follow up was noted in early studies. Early open maintenance study had reported that schizophrenic patients who received risperidone 0.5-22.5 mg/day, for 1 year showed at least 50% reduction in total BPRS scores in 62% of cases, and 37% had at least 75% reduction in their scores (Mertens, 1991).

Another important issue which needs to be addressed is the utility of risperidone in refractory cases. In our study it was interesting to note that, the average duration of schizophrenic disease was 6.92 years and many of these patients were resistant to the previously administered antipsychotic therapy, in spite of this fact over 66% of the patients were considered as responders to risperidone, with the reduction of at least 20% in their total PANSS scores. Over 66% of patients were considered as not ill or very mildly ill at the end of the 16 weeks of therapy. There was a rise in the mean weight at the end of the trial as compared to the basal level, with risperidone therapy.

Extrapyramidal side effects probably pose the most important measurable acute problem with conventional neuroleptics. Such acute symptoms are also important because dystonic reactions are certainly alarming to the patients, parkinsonian tremor can be embarrassing, and akinesia may further complicate schizophrenic apathy (Janicak, 1994). Apart from that virtually all schizophrenic patients will be on indefinite maintenance drug therapy; therefore, one must be concerned about adverse events that arise with a long term drug exposure. A

multicentre long term study (Lindstrom *et al.*, 1995) with risperidone, in Sweden, with 88 patients observed that treatment of schizophrenic patients with risperidone for 1 and 2 years was associated with significant reductions in positive, negative, excited, and cognitive symptoms; a significant amelioration of extrapyramidal symptoms; improved social functioning; and a significant reduction in days spent in the hospital and thus in treatment costs. For the average patient, both the avoidance of EPS and optimal efficacy appear to occur at doses in the 2-8 mg range (Davis & Janicak, 1996). The much lower incidence of EPS with risperidone, compared with haloperidol, has been reported (Claus *et al.*, 1992 & Chouinard *et al.*, 1993). Patients in risperidone treatment groups reported an incidence of adverse side effects which was equal to or slightly greater than that observed in the placebo group. No treatment dependent trends in laboratory, electrocardiogram, or vital signs measures were noted, and no serious side effects were reported.

In our study, though, adverse effects were reported by 40% of the patients, they were mild. No serious side effects reported in any of the patients. Even the Extrapyramidal Symptoms (EPS) which were seen in some of the patients were well controlled either by reducing the dose of risperidone or with trihexyphenidyl hydrochloride tablets administration. There was no worsening of the extrapyramidal rating scale scores at any of the time in the trial which further endorses the safety of the drug. The efficacy and safety was further reflected in the fact that the patients who had completed the trial as per the protocol for 16 weeks still insisted on continuing with the drug and were continuing to enjoy the relief of the symptoms. There were no significant changes in any of the other safety parameters studied during the trial.

The authors found risperidone to be significantly useful in the treatment of schizophrenia. Its administration lead to improvement in the wide range of symptoms, including the negative symptoms.

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REFERENCES

- Addington, D.E., Jones, B. & Bloom, D. (1993) Reduction of hospital days in chronic schizophrenic patients treated with risperidone: A retrospective study; Reprinted from *Clinical Therapeutics*, 15, 917-926.
- Chouinard, G., Jones, B., Remington, G., Bloom, D., Addington, D., Macewan, G.W., Lebel, A., Beauclair, L. & Arnot, W. (1993) A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *Journal of Clinical Psychopharmacology*, 13, 25-35.
- Chouinard, G., Ross-Chouinard, A., Annable, L. & Jones, B.D. (1980) The extrapyramidal symptom rating scale. *Canadian Journal of Neurological Sciences*, 7, 23-30.
- Claus, A., Bollem, H., De Cuyper, H., Eneman, M., Malfroid, M., Peuskens, J. & Heylen, S. (1992) Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. *Acta Psychiatr Scand.*, 85, 295-305.
- Davis, J.M. & Janicak, P.G. (1996) Risperidone: a new, Novel (and Better?) Antipsychotic. *Psychiatric Annals*. 26 (2), 78-87.
- Grant, S. & Kitton, A. (1994) Risperidone: a review of its pharmacology and therapeutic potential in the treatment of schizophrenia. *Drugs*, 48 (2), 253-273.
- Janicak, P.G. (1994) Principles and practice of psychopharmacotherapy, (Ed.) Janicak PG 1 (1).
- Kay, S.R., Opler, L.A. & Fiszbein, A. (1992) Positive and negative syndrome scale Manual. Published by Multi-Health System, Inc. U.S.A.
- Lindstrom, E., Eriksson, B., Heelgren, A., Knorrning, L.V. & Eberhard, G. (1995) Efficacy and safety of risperidone in the long-term treatment of patients with schizophrenia. *Clinical Therapeutics*, 17 (3), 402-412.
- Mertens, C. (1991) Long term treatment of chronic schizophrenic patients with risperidone. In: *Risperidone: major progress in antipsychotic treatment*. (Ed.) Kane, J.M., pp 44-48, Oxford: Oxford Clinical Communications.

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