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RISPERIDONE IN INDIAN PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

Conventional antipsychotic agents are not effective against negative symptoms of schizophrenia and are also noted for their extrapyramidal side effects. Risperidone is a noval antipsychotic agent whose dual antagonism of dopamine and serotonin receptors is believed to underlie its efficacy against negative symptoms and the low incidence of extrapyramidal side effects. An open, non-comparative study of seven weeks duration was performed to evaluate risperidone in the treatment of schizophrenia in Indian patients. Previous antipsychotic therapy was discontinued for a week before risperidone therapy was initiated. At the end of six weeks of risperidone therapy, clinical improvement (≥ 20% reduction in total score on positive and negative syndrome scale for schizophrenia (PANSS)) was shown by 128 (87.7%) of the 146 evaluable patients. Statistically significant reduction ($p < 0.05$) occurred in the total score of this scale and in the subscale scores for positive, negative and general psychopathology symptoms and in the clinical global impression severity score. The number of patients with adverse experiences were 108 (65.5%) at baseline and 120 (72.7%) at the end of risperidone therapy. Extrapyramidal symptoms, seen in 65 (39.4%) patients compared to 22 (13.3%) patients at baseline, were largely mild to moderate in intensity.

Key words : Risperidone, novel antipsychotic agents, Indian patients, schizophrenia, PANSS, clinical improvement

Neuroleptics are considered to be the cornerstone in the treatment of schizophrenia. However their efficacy in controlling the positive symptoms of schizophrenia is offset by their relative lack of effect on negative symptoms such as blunted affect, emotional withdrawal, low motivation and drive, poor rapport and social withdrawal, further the potent dopamine antagonism exhibited by these agent is associated with a high occurrence of extrapyramidal symptoms. There has been a long-felt need for a drug effective against negative as well as positive symptoms with a lower propensity to cause extrapyramidal symptoms. A serotonin receptor antagonist added to a dopamine receptor antagonist, can improve psychotic symptoms (Reyntjens et al., 1986) and also alleviate neuroleptic induced parkinsonian side effects (Bersani et al., 1986; Hilderbrand and Delecluse, 1987; Bersani et al., 1990). It has also been suggested that serotonin antagonism may improve the negative symptoms of schizophrenia (Bleich et al., 1988).

Risperidone, a benzisoxazole derivative is noval antipsychotic agent and chemically unrelated to conventional antipsychotics. It has blocking effects both on $5HT_2$ and dopamine D_2 receptors (Leysen et al., 1988; Janssen et

al., 1988). Animal experiments have indicated its low potency in inducing extrapyramidal symptoms (EPS) (Megens et al., 1988). Early clinical trials suggested that risperidone is effective on both positive and negative symptoms of schizophrenia and causes a lower incidence of EPS (Roose et al., 1988; Gelders et al., 1990). Subsequent double blind studies comparing it with haloperidol and perphanazine have confirmed these results (Heylen & Gelders, 1988; Claus et al., 1992; Hoyberg et al., 1993). Ceskova and Svestka (1993), Borison et al. (1992), Davis & Janicak (1994), Marder (1996) have further proved the clinical efficacy of risperidone. Side effect profile of risperidone show that it produces less EPS in lower dosage but at higher dosage the rate of EPS is similar to haloperidol. However in the US-Canada study the patients receiving risperidone 6 mg/day required same amount of antiparkinsonian medication as those on haloperidol.

Risperidone has been extensively tried in the west yet the drugs efficacy and tolerability in Indian patients has not been established. The present study was therefore undertaken with the following aims.

1. To assess the efficacy of risperidone in Indian patients suffering from schizophrenia.
2. To study the side effect profile of risperidone.

MATERIAL & METHOD

Inclusion criteria : Age between 16 and 65 years, either sex; diagnosis of schizophrenia according to DSM-IV criteria; informed consent from patients, or their relatives or legal guardians

Exclusion criteria : Patients with clinically significant cardiac or heamatological disorders or with abnormal renal or hepatic laboratory tests ; pregnant or lactating women; patients with mental disorders other than chronic schizophrenia or acute exacerbation of chronic schizophrenia; patients who had received depot neuroleptics less than 4 weeks before entry into the study; patients with a history of alcohol or drug abuse; history of hypersensitivity to benzisoxazoles; patients with Parkinson's disease, narrow angle glaucoma or prostatic hypertrophy; patients who had a reduction of 20% in total PANSS score after 1 week of placebo therapy.

Medication : The starting dose was 1 mg b.i.d. on day 1, stepped upto 2 mg b.i.d. on day 2 and 3 mg b.i.d. thereafter for 3 weeks. At the end of 3 weeks, the dose was stepped up to 4 mg b.i.d. in patients who showed a reduction of <20% in total PANSS score; others continued to receive 3 mg b.i.d. Completion of 6 weeks of active therapy with risperidone marked the end of the study for each patient.

Assessment : Assessment were made at weekly intervals on PANSS. Clinical improvement was defined as reduction of > 20% in total PANSS score. The overall severity of illness was also assessed on the Clinical Global Impression (CGI) scale.

The Scandinavia Society of Pharmacology Committee on Clinical Investigations Scale (UKU Scale) was used to assess side effects.

As it was a multicentric study all investigators met for one day to establish uniformity across centres.

RESULTS

One hundred and seventy-seven patients were enrolled in this study at 6 centres in India. Eight patients did not receive active medication and four others who had received active medication did not report for post-therapy evaluations. Seventeen patients were lost to follow-up. One hundred forty six patients completed the study per protocol.

The demographic and clinical profile of patients is shown in table 1. Clinical improvement (reduction of 20% or more in PANSS total score) in the intent to treat and per protocol population is shown in table 2.

In the per protocol population, 75 patients received risperidone 3 mg b.i.d. for 6 weeks and in 71 patients the dose was stepped up from 3 mg b.i.d. to 4 mg b.i.d. due to inadequate

TABLE 1
PATIENTS CHARACTERISTICS ON STUDY ADMISSION - INTENT TO TREAT POPULATION (N=165)

Characterstics	Number of patients (%)
Sex	
Male	97 (58.8%)
Female	68 (41.2%)
Age (yrs.)	
Mean±S.D.	31.93±7.94
Range	17-57
Treatment status	
Outpatients	76 (46.1%)
Inpatients	89 (53.9%)
Duration of disease	
<5 yrs.	86
≥ 5yrs. to ≤ 10 yrs.	51
>10 yrs.	28
Prior hospitalizations	
Yes	82 (49.7%)
No	83 (50.3%)
Number of prior admissions	
(Range)	1-12
Patients resistant ot previous antipsychotics	
Yes	26
No	105
Data not available	34
DSM-IV classification according to longitudinal course**	
-Episodic with inter-episode residual symptoms	60
-Episodic with no inter-episode residual symptoms	9
-Continuous	92
-Unspecified pattern	2

* 2 patients were not classified as the duration of disease was less than 1 year

** Resistance to therapy is defined as non response to two different antipsychotic drugs given in adequate dosage for a period of 6 weeks

response at the end of three weeks. The clinical improvement achieved by these patients is shown in table 3.

The reduction at the end of risperidone

TABLE 2
CLINICAL IMPROVEMENT WITH RISPERIDONE THERAPY

	Number (%) of patients showing clinical improvement i.e. ≥20% reduction in PANSS total score
Intent to treat	128/165 (77.6%)
Per protocol (evaluable)	128 /146 (87.7%)

TABLE 3
CLINICAL IMPROVEMENT WITH RISPERIDONE 3 mg B.I.D. AND RISPERIDONE 4 mg B.I.D. (N=146)

	Number (%) of patients showing clinical improvement i.e ≥20% reduction in PANSS total score
Response to risperidone 3 mg b.i.d. for 6 weeks	71/146 (48.6%)
Cumulative response to risperidone 3 mg b.i.d. for 3 weeks followed by 3 or 4 mg b.i.d. for 3 weeks	128/146 (87.7%)

therapy in PANSS total score, PANSS positive subscale score, PANSS negative subscale score and CGI severity are shown in table 4 and 5.

Clinical improvement was also seen in 17 of the 25 patients refractory to treatment with haloperidol, chlorpromazine, trifluoperazine, fluphenazine or pimozide used alone or in combination. One of the resistant patient discontinued treatment. Adverse events were recorded on the Scandinavian Society of Psychopharmacology Committee of Clinical Investigations (UKU) side effects rating scale (Table 6 & 8).

The majority of adverse events were mild to moderate in intensity. However, a decrease intensity was noted in some of the adverse events which were of severe intensity at baseline : five patients with decreased duration of sleep, four patients with emotional indifference, three patients with tension/inner unrest, three patients with decreased sexual desire and one patient with decreased duration of sleep. In these patients intensity was reduced to mild or

TABLE 4
RESPONSE TO RISPERIDONE 3 MG B.I.D. FOR 6 WEEKS (N=76)

Scale	Mean±SD
Total PANSS	
Baseline	78.43±15.90
End of therapy	44.61±11.84
Reduction	33.81±13.95*
Positive PANSS	
Baseline	20.84±5.57
End of therapy	9.92±3.80
Reduction	10.92±5.74*
Negative PANSS	
Baseline	20.03±7.00
End of therapy	11.35±3.35
Reduction	8.68±5.94*
General psychopathology PANSS	
Baseline	37.56±9.12
End of therapy	23.35±6.40
Reduction	14.21±7.19*
CGI Severity	
Baseline	3.63±0.70
End of therapy	1.63±0.87
Reduction	2.00±1.05*

* significant p<0.0001

moderate except in one patient who reported decreased duration of sleep.

A fall of 10 mmHg in systolic blood pressure occurred in one patient who had transient orthostatic dizziness.

One case of the overdosage with trihexyphenidyl occurred during the study (twenty five tablets of trihexyphenidyl).This patient was delerious for 1 day. He was managed conservatively and risperidone was restarted after 2 days. This patients also had allergic rhinitis with nasal congestion, sinusitis and a single episode of bronchial asthma.

One patient requested to be withdrawn from study after 1 week of risperidone therapy. He developed tension/inner unrest, akathisia, reduced salivation of severe intensity, tremor, rigidity and polyuria/polydipsia of moderate intensity. Trihexyphenidyl for parkinsonian symptoms was required in 72 (47.4%) patients, lorazepam for sedation in 51 (30.9%) patients

TABLE 5
RESPONSE TO RISPERIDONE 3 mg B.I.D. FOR 3 WEEKS FOLLOWED BY RISPERIDONE 4 mg B.I.D. FOR 3 WEEKS (N=71)

Scale	Mean±SD
Total PANSS	
Baseline	80.31±16.39
End of therapy	54.68±15.88
Reduction	25.63±14.64*
Positive PANSS	
Baseline	20.45±5.63
End of therapy	12.23±4.94
Reduction	8.23±5.78*
Negative PANSS	
Baseline	20.18±8.15
End of therapy	14.82±6.55
Reduction	5.37±4.74*
General psychopathology PANSS	39.68±8.63
Baseline	27.63±7.65
End of therapy	12.04±7.55*
Reduction	
CGI Severity	
Baseline	3.75±0.84
End of therapy	2.42±0.10
Reduction	1.32±1.19*

* significant p<0.001

TABLE 6
ADVERSE EVENTS AT BASELINE AND AT THE END OF SIX WEEKS OF RISPERIDONE THERAPY (N=165)

Adverse events (AE)	No. (%) patients with AE at baseline	No. (%) of patients with AE at the end of risperidone therapy*
Extrapyramidal AE	22 (13.3)	65 (39.4)
Psychic AE	100 (60.6)	101 (61.2)
Autonomic AE	33 (20)	54 (37.7)
Other AE	31(18.2)	33 (20)
Total no. of patients with AE	108 (65.5)	120 (72.7)

* Patients with AE at baseline are included

and propranalol for control of tremor in 7 (4.2%) patients. Some patients needed more than one of the above medications.

DISCUSSION

The clinical efficacy and tolerability

TABLE 7
ADVERSE EVENTS (AE) PRESENT AT BASELINE BUT IMPROVING/DISAPPEARING WITH RISPERIDONE THERAPY (N=165)

Adverse events	No. (%) of patients with AE at baseline	No. (%) of patients with AE at the end of therapy*
Extrapyramidal		
Dystonia	1 (0.6)	0
Hyperkinesia	2 (1.2)	1 (0.6)
Psychic		
Concentration difficulties	57 (34.5)	36 (21.8)
Depression	35 (21.2)	18 (10.9)
Tension/Inner unrest	45 (27.3)	34 (20.6)
Reduced duration of sleep	59 (35.8)	21 (12.7)
Emotional indifference		
Failing memory	66 (40)	42 (25.5)
Decreased dream activity	9 (5.5)	3 (1.8)
Increased dream activity	8 (4.8)	2 (1.2)
Autonomic		
Reduced salivation	13 (7.9)	8 (4.8)
Nausea/vomiting	10 (6.1)	6 (3.6)
Constipation	11 (6.7)	3 (1.8)
Diarrhoea	1 (0.6)	0
Other		
Rash	4 (2.4)	2 (1.2)
Pruritus	3 (1.8)	2 (1.2)
Diminished sexual desire	15 (9.1)	4 (2.4)
Headache	12 (7.3)	8 (4.8)
Amenorrhoea	11 (6.7)	10 (6)
Galactorrhoea	2 (1.2)	0
Increased sexual desire	3 (1.8)	1 (0.6)
Organic dysfunction	1 (0.6)	0

* Patients with AE at baseline are included

TABLE 8
ADVERSE EVENTS AT BASELINE AND AFTER RISPERIDONE THERAPY (N=87)

Adverse events	No (%) of patients with AE at baseline	No. (%) of patients with AE at the end of therapy*
Extrapyramidal AE**		
Rigidity	0	18 (10.9)
Hypokinesia/akinesia	9 (5.5)	29 (17.6)
Tremor***	12 (7.3)	37 (22.4)
Akathisia	1 (0.6)	14 (8.5)
Psychic AE		
Asthenia/lassitude/ increased fatiguability	48 (29.1)	78 (47.3)
Sleepiness/sedation	13 (7.9)	21 (12.7)
Increased duration of sleep	8 (4.8)	10 (6)
Psychic dependence	3 (1.8)	3 (1.8)
Autonomic AE		
Accomodation disturbances	0	8 (4.8)
Increased salivation	2 (1.2)	20 (12.1)
Micturition disturbance	1 (0.6)	2 (1.2)
Orthostatic dizziness	6 (3.6)	11 (6.7)
Palpitation/tachycardia	6 (3.6)	11 (6.7)
Increased tendency to sweating	2 (1.2)	2 (1.2)
Polyuria/Polydipsia	11 (6.7)	11 (6.7)
Other		
Weight gain	0	11 (6.7)
Weight loss	0	1 (0.6)
Erectic dysfunction	1(0.6)	4 (2.4)
Ejaculation dysfunction	1 (0.6)	2 (1.2)

* Patients with AE at baseline are included
** Mild dystonia was recorded in 8 patients during week 1 and week 2
*** Patients who had only mild clinically non-significant tremor are excluded

of risperidone therapy observed in the present study is in line with other studies demonstrating that risperidone is an effective and well tolerated antipsychotic (Kane et al., 1988; Leysen et al., 1988; Megens et al., 1988; Muller-Spahn, 1992). In 71 of the 146 patients in this study a risperidone dosage of 3 mg b.i.d. was sufficient to produce clinically significant improvement. Out of the 71 patients who had their dose stepped up to 4 mg b.i.d. 57 patients (80%) showed significant clinical improvement. Statistically significant reductions ($p<0.05$) occurred in the total score, positive, negative and general psychopathology subscale score on PANSS and in CGI severity scores. Of particular interest is the improvement in all the seven negative symptoms on PANSS which has

not been reported with other antipsychotics; this is of importance because the only other antipsychotic effective against negative symptoms viz. clozapine poses the risk of a serious adverse event (agranulocytosis) ; it is therefore not suitable for all patients and involves practical difficulties in usage-the need to perform weekly WBC count (Roose et al., 1988). Patients refractory to other antipsychotics viz. haloperidol, chlorpromazine, trifluoperazine, fluphenazine & pimozide used alone or in combinations also posted significant responses.

Adverse experiences were already present in 65.7% patients at baseline i.e. after a washout period of one week from previous antipsychotic medication; this increased to 72.7% of patients at the end of therapy. Extrapyramidal symptoms were largely mild to moderate in intensity and need for antiparkinsonian medication was considerably lower than reported for conventional antipsychotics. Concentration difficulties, depression, reduced duration of sleep, tension/inner unrest, emotional indifference, diminished sexual desire and headache improved with risperidone therapy in a number of patients. Increased salivation and postural dizziness seen in 12.1% and 6.7% patients respectively were largely mild to moderate and transient. A fall in systolic blood pressure of 10 mmHg with postural dizziness was seen in 1 patients only. Only one patient requested to be withdrawn because of severe adverse events. There were no serious adverse events. Thus risperidone was well tolerated. Increasing the dosage from 3 mg b.i.d. to 4 mg b.i.d. resulted in a somewhat higher incidence of adverse events but resulted in a greater proportion of patients responding to risperidone therapy.

In conclusion, risperidone was effective in the treatment of Indian patients with schizophrenia. Both positive and negative symptoms were ameliorated. Clinical improvement was noted in 87.7% of patients by the end of 6 weeks of risperidone therapy. Risperidone was effective in 17 of the 25 patients refractory to treatment with haloperidol, chlorpromazine, trifluoperazine, fluphenazine or pimozide used alone or in combination.

The drug was well tolerated. Side effects were largely mild to moderate in intensity. Extrapyramidal symptoms and need for antiparkinsonian medication were considerably lower than reported for conventional antipsychotics.

Because of its high efficacy, relief of negative symptoms, efficacy in patients refractory to conventional antipsychotics, good tolerability and freedom from serious adverse events risperidone would be an important antipsychotic drug for the treatment of schizophrenia in Indian patients.

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