

## ONCE DAILY RISPERIDONE IN TREATMENT OF SCHIZOPHRENIA

VIVEK AGARWAL & RAKESH K. CHADDA

### ABSTRACT

Forty four schizophrenic patients were randomly assigned to receive risperidone in 4-8 mg doses either once daily or twice daily for 8 weeks. An open trial was conducted to determine the efficacy of once daily administration of risperidone as compared to twice daily administration. Assessment were done on Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) scale. Eighty two percent of the once daily patients and 79% of the twice daily patients showed a significant treatment response. No significant differences were observed between the two groups in response pattern and adverse effects at the end point. Risperidone given once daily was as effective as twice daily administration.

*Key words :* Risperidone, schizophrenia, dose-frequency

Risperidone, a potent serotonin (5HT<sub>2</sub>) and dopamine (D<sub>2</sub>) receptor blocker, has been shown to be an effective antipsychotic in patients of schizophrenia (Chouinard et al., 1993; Marder and Meibach, 1994; Agarwal et al., 1998).

The largest multicentre study of risperidone of 1362 patients reported risperidone to have a bell shaped dose-response curve peaking at about 4 mg/day for its therapeutic effects (Muller-Spahn, 1992). In the later studies also (Kleiser et al., 1995; Molier et al., 1997), optimal dose of risperidone in terms of both efficacy and safety has been found to be 4 mg/day which, however, could be increased to 6-8 mg/day if required.

In clinical trials risperidone has been given twice daily mainly to minimise the risk of orthostatic hypotension. However, in clinical usage orthostatic hypotension has not been the major problem. The mean combined half-life of risperidone and its activity metabolite 9-hydroxy risperidone is about 20 hours (Owens et al., 1998) and it can be administered once daily. Once daily administration is more convenient and also improves compliance (Weiden et al., 1995).

The present study was carried out to compare the therapeutic efficacy of once daily and twice daily administration of risperidone in schizophrenic patients.

### MATERIAL AND METHOD

The study was conducted in outpatient setting at the Institute of Human Behaviour and Allied Sciences, Delhi. Patients with provisional diagnosis of schizophrenia attending the outpatient services on the two particular week days (corresponding to the clinical unit) were screened for the purpose of study during the period of July 1998 to July 1999. ICD-10 criteria were used to screen the patient. Diagnosis was made by chart review and clinical interview. Patients with age less than 18 years, comorbid axis 1 disorder or psychoactive substance abuse, pregnant or lactating mothers, clinically significant organic or neurological disorder and with abnormal electrocardiogram findings were excluded. Patients were also excluded if they refused to take oral medication, had been given depot neuroleptic 15 days prior to trial or the

## ONCE DAILY RISPERIDONE IN SCHIZOPHRENIA

investigational drug in 4 weeks prior to trial. Oral informed consent was taken from patients or guardian, whichever applicable. Consenting patients with diagnosis of schizophrenia were taken for study. Patients were either drug naive or were given one week washout if on any oral neuroleptic.

At baseline detailed psychiatric and medical history was recorded and physical examination was carried out. Routine laboratory investigations and electrocardiogram was done. Psychopathology was assessed on PANSS (Kay et al., 1987) and CGI (NIMH, 1985). Adverse effects were assessed on Dosage Record Treatment Emergent Symptom Scale (DOTES; Campbell and Palij, 1985). Patients were assessed on these scales at baseline and thereafter at week 1, 2, 4, 6, and 8.

Patients were randomly assigned to either once daily or twice daily risperidone group. Risperidone dosages was increased from 2 mg/day on day 1 to 4 mg/day on day 2. Thereafter patients were maintained on 4 mg/day dosage till 4 weeks and increased to 6 mg/day and 8 mg/day from 5th and 7th week respectively if the patient did not show atleast 20% reduction in PANSS baseline scores. In once daily group, risperidone was given in the evening while in twice daily group it was given in morning and evening in equally divided doses. The total duration of trial was 8 weeks.

Data was analysed using Intent-to-treat analysis. Data of all the patients was analysed who were treated for atleast 14 days. The end point score was defined as last observed score. Baseline and end point scores were compared using paired t-test (two tailed) for within group comparisons and t-test for independent samples for between group comparisons.

### RESULTS

Forty four patients consented for the study and were taken for the trial. This included twenty three patients (14 male/9 female) in the once daily group and 21 (13 male/8 female) patients

in the twice daily group. Two once daily patients discontinued the medication because of adverse effects while one discontinued the medication because of lack of response. One twice daily patient discontinued medication because of adverse effects while two were lost to follow-up. Thus, twenty once daily and 18 twice daily patients completed the trial. Mean age (range) was 34 (18-50) years in once daily and 37 (20-60) years in twice daily group while duration of illness (mean $\pm$ SE) was 5 $\pm$ 0.9 years and 5.9 $\pm$ 1.1 years respectively. Both the groups were comparable with respect to age, sex and duration of illness. Mean risperidone dose was 5 $\pm$ 0.3 mg in once daily group and 5.3 $\pm$ 0.3 mg in twice daily group. Concomitant medication given were antiparkinsonian drugs in 48% once daily and 47% twice daily patients and benzodiazepine for sedation in 17% once daily and 26% twice daily patients. According to intent to treat analysis data of 23 once daily and 19 twice daily patients was analysed as two twice daily patients lost to follow up in first week of trial.

Improvement was observed both on PANSS as well as on the CGI. Eighty two percent of subjects in the once daily group and 79% in the twice daily group (showed a 20% or greater reduction in total PANSS score at end point). Mean total PANSS scores were reduced from 84.8 at baseline to 53.2 at end point in once daily group and from 78.7 to 46.2 in twice daily group. PANSS total and subscale scores showed a significant improvement ( $p < 0.0001$ ) from baseline to endpoint in each treatment group. The two groups did not differ in respect of improvement on total PANSS as well as subscale scores (Table).

Severity of illness as assessed on CGI reduced from 5.0 $\pm$ 0.2 to 3.3 $\pm$ 0.2 in once daily group and 4.5 $\pm$ 0.2 to 2.8 $\pm$ 0.2 in twice daily group. No significant difference was found between the two groups. Mean CGI-improvement was 2.1 in both the groups at endpoint. Eighty two percent once daily and 79% twice daily patients had ratings between 1 to 3; 18% and 21% respectively had rating of 4.

## VIVEK AGARWAL & RAKESH K. CHADDA

**TABLE**  
**MEAN ( $\pm$ SE) CHANGES IN SCORES OF PANSS FROM BASELINE IN PATIENTS**  
**RECEIVING RISPERIDONE ONCE DAILY AND TWICE DAILY**

PANSS*	Baseline		Changes vs. baseline <sup>b</sup>		P <sup>c</sup>
	Once daily	Twice daily	Once daily	Twice daily	
Total	84.8 $\pm$ 1.9	78.7 $\pm$ 2.4	31.6 $\pm$ 3.2	32.5 $\pm$ 4.0	ns
Positive	23.2 $\pm$ 1.0	21.8 $\pm$ 1.3	10.4 $\pm$ 1.1	10.4 $\pm$ 1.5	ns
Negative	23.3 $\pm$ 1.6	21.2 $\pm$ 1.7	8.1 $\pm$ 1.2	8.4 $\pm$ 1.3	ns
General					
Psychopathology	38.3 $\pm$ 1.3	35.8 $\pm$ 1.4	13.1 $\pm$ 1.5	13.8 $\pm$ 1.8	ns

a) PANSS - Positive and Negative Syndrome Scale

b) All changes from baseline were significant ( $p < 0.0001$ ) in both the groups

c) Significance of differences in change in once daily vs. twice daily group.

At least one adverse effect was reported by 14 (61%) patients in the once daily group and 13 (68%) in the twice daily group. Extrapyramidal syndrome, anxiety and insomnia were the commonest adverse effects reported by the patients, seen in 11, 3 and 3 once daily group patients respectively and 9, 4 and 4 twice daily group patients respectively. Severe adverse effects included extrapyramidal syndrome in three patients (one in once daily and two in twice daily group, insomnia in one in twice daily group) and urinary incontinence in one patient in each group. One once daily patient had discontinued the drug because of urinary incontinence and the other discontinued due to amenorrhea. One twice daily patient discontinued the drug because of urinary incontinence. Changes in blood pressure and heart rate were observed in both the groups but were not clinically significant.

### DISCUSSION

Risperidone in once daily regime was as effective as the twice daily regime in producing improvement in patients of schizophrenia. Once daily regime was not also associated with any additional adverse effects especially the increased rate of orthostatic hypotension apprehensions about which have been mentioned in the earlier literature. The response rate was similar in once daily (82%) and twice daily (79%) groups. Further, no statistically significant difference was found on PANSS total and subscale scores at the endpoint, between

the groups. Also, CGI severity and improvement scores were comparable at the end point for both the groups. No significant difference was seen in respect to extrapyramidal symptoms (48% in once daily and 47% in twice daily group) and other adverse effects between the groups. Dropout rates were also comparable in both the groups (13% once daily and 14% twice daily patients). Only two once daily and one twice daily patient discontinued the drug because of adverse effects. These findings show that once daily administration of risperidone is as safe and well tolerated as twice daily administration. Risperidone is administered twice daily mainly because of orthostatic hypotension. However, in clinical practice orthostatic hypotension was not the major problem and in this study also none of the patient developed orthostatic hypotension in both the groups. Adverse effects of the drugs and complex treatment regime are two important causes of non-compliance with treatment in the schizophrenic patients (Marder, 1998), which subsequently lead to relapse of the illness. Therefore, simple regimes like once daily administration of risperidone will be convenient to the patients and would improve compliance (Weiden et al. 1995).

Limitation of the study were open trial, small sample size and absence of control group.

The findings suggest that once daily administration of risperidone is safe and effective. Further controlled trials on larger sample with comparison of blood levels of risperidone are required to confirm the findings.

## ONCE DAILY RISPERIDONE IN SCHIZOPHRENIA

### REFERENCES

- Agarwal, A.K., Bashyam, V.S.P., Channabasavanna, S.M., Dhavale, H.S., Khan, M.A.M., Khanna, S., Pradhan, P.V., Katiyar, M., Rajkumar, R., Niazi, F.R., Jalali, R.K., Gowrishankar, R., Mishra, S.K. & Sood, O.P. (1998) Risperidone in Indian patients with schizophrenia. *Indian Journal of Psychiatry*, 40, 3, 247-253.
- Campbell, M. & Palij, M. (1985) Measurement of side effects including tardive dyskinesia. *Psychopharmacology Bulletin*, 21, 4, 1063-1066.
- Chouinard, G., Jones, B., Remington, G., Bloom, D., Addington, D., MacEvan, G.W., Labelle, A., Beauclair, L. & Arnott, W.A. (1993) A Canadian multicentre placebo controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *Journal of Clinical Psychopharmacology*, 13, 25-40.
- Kay, S.R., Fiszbein, A. & Opler, L.A. (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, 13, 261-276.
- Kleiser, E., Lehmann, E. & Kinzler, E. (1995) Randomized, double blind controlled trial of risperidone versus clozapine in patients with chronic schizophrenia. *Journal of Clinical Psychopharmacology*, 15, 45-57.
- Marder, S.R. (1998) Facilitating compliance with antipsychotic medication. *Journal of Clinical Psychiatry*, 59, (suppl. 3), 21-25.
- Marder, S.R. & Meibach, R.C. (1994) Risperidone in the treatment of schizophrenia. *American Journal of Psychiatry*, 151, 825-835.
- Moller, H.J., Bauml, J. & Einzler, F. (1997) Risperidone in the treatment of schizophrenia : results of a study of patients from Germany, Austria and Switzerland. *European Archives of Psychiatry and Clinical Neurosciences*, 246, 291-296.
- Muller-Spahn, F. (1992) Risperidone in the treatment of schizophrenic patients : an international double blind parallel group study versus haloperidol (abstract). *Clinical Neuropharmacology*, 15 (suppl), 90A-91A.
- National Institute of Mental Health (1985) Clinical Global Impression Scale. *Psychopharmacology Bulletin*, 21, 4, 839-841.
- Owens, M.J. & Risch, S.C. (1998) Atypical antipsychotics. In : *Textbook of Psychopharmacology*, End. 2. (Eds.) Schatzberg, A.F. & Nemeroff, C.B., pp 323-348, The American Psychiatric Press, Inc.
- Weiden, P.J., Mott, T. & Curcio, N. (1995) Recognition and management of neuroleptic non-compliance. In : *Contemporary issues in the treatment of schizophrenia*, (Eds.) Shrikui, G.L., Nasrallah, H.A., pp 411-434, American Psychiatric Press, Inc.

---

VIVEK AGARWAL\*, MD, Senior Resident & RAKESH K. CHADDA, MD, MAMS, Additional Professor, Department of Psychiatry, Institute of Human Behaviour & Allied Sciences, P.O. Box -9520, Dilshad Garden, Delhi - 110 095.

\* Correspondence