Indian Journal of Psychiatry, 2002,44(4),365-371

COMPARATIVE EFFICACY OF CENTBUTINDOLE & RISPERIDONE IN SCHIZOPHRENIA

R.CHANDRA, H. SINGH , P.K. DALAL, O.P. ASTHANA & J.S.SRIVASTAVA

ABSTRACT

Centbutindole is a new antipsychotic agent related to butyrophenone group. The drug is dopamine antagonist but it also blocks 5HT$_2$ receptors. Clinically the drug has passed through phase I, II & III clinical trials successfully and it has shown effective antipsychotic activity in schizophrenic patients. In the present study the drug was compared with risperidone in a double blind manner for a period of 8 weeks to assess the efficacy in schizophrenic patients.Patients of schizophrenia evaluated on PANSS, CGI & UKU side effect rating scale weekly. Out of 44 patients included in study,38 completed the trial. The intergroup comparison of two drugs showed that centbudindole and risperidone have similar onset of antipsychotic action as both the drugs showed significant decrease in the total PANSS score as well as positive syndrome score, negative syndrome score and general psychopathology score from 2nd week onwards. The scores in both the groups showed a steady and significant decline from 2nd week to 8th week of study. The present study showed that centbutindole has similar improvement on clinical global impression with risperidone. The side effect profile was similar in the two drugs except dystonia (5 patients in centbutindole vs 1 patient in risperidone group). The findings of present study shows that Centbutindole could be used as a promising new drug for treatment of schizophrenia in place of a typical antipsychotics as it has shown improvement on negative symptoms similar to risperidone.

Key Words: Centbutindole, Risperidone, Atypical Antipsychotics and Extrapyramidal symptoms

Centbutindole is a new antipsychotic (compound 70/343) 2-[Y-(P-fluorobenzoyl)Propyl]-1,2,3,4,6,7,12,12a octahydro pyrazino (2',1',:6,1) pyrido (3-4-β) indole related to butyrophenone group (Saxena et al.,1973). It is a light yellow crystalline compound with molecular weight of 391.49 which is soluble in dilute acids or organic compounds.

Preclinically it has been found to block amphetamine induced hyper activity/stereotypy and secondary conditioned avoidance responses.These effects have been found in doses lower than those required for chlorpromazine and haloperidol. The drug is primarily a dopamine antagonist but it also blocks 5HT$_2$ receptors (Gulati et al.,1988). The L-isomer of centbutindole is many times more active than the d-isomer (Singh et al.,1977). Clinically the drug has passed through phase I, II & III clinical trials successfully and it has shown effective antipsychotic activity in schizophrenic patients (Doonga ji et al ,1983). The peak serum levels were reached at 4 hours and the plasma half life was 12 hours(Paliwal et al.,1992). The present study has been conducted with aims to compare the antipsychotic efficacy with regards to positive and negative symptoms of schizophrenia as well as side effect profile of centbutindole and risperidone.

MATERIAL AND METHOD

A comparative double blind trial was designed. Stringent selection criteria were applied in this study to obtain a homogenous sample. The subjects were schizophrenic patients diagnosed according to ICD-10 DCR criteria. Patients satisfying both the inclusion and exclusion criteria were admitted in the hospital and randomized according to a predetermined randomization schedule to receive either centbutindole or risperidone for a period of 8 weeks. Patient were assessed weekly for clinical symptomatology and side effects. The patients of schizophrenia having no prior drug treatment between age of 18 to 50 years, willing to accept oral medication were included in the study. Patients with hyper sensitivity to study drug, pregnancy or lactation, coexisting severe organic disease, depression, drug abuse or mental subnormality and patients requiring parenteral medication or ECT were excluded from the study. Each patient/guardian gave informed written consent before inclusion in the study. The eligible patients were subjected to a detailed base line clinical , hematological and biochemical investigations. There patietns were randomly allocated to receive either 4.5mg of centbutindole or 6 mg of risperidone. The drug was formulated in capsules identical in colour, shape and size. Each capsule contained centbutidole (1.5 mg) or risperidone (2 mg). Initial dose was 1 Capsule twice a day for three days increasing to 1 capsule in the morning and 2 capsule at bed time through out the study period of 8 weeks.During this study period each patient was evaluated on positive and negative syndrome scale (PANSS), clinical global impression scale and UKU side effect rating scale. At the end of the study period i.e. 8th week patients were evaluated again by detailed history, physical examination and laboratory investigations to determine any changes in the physical or biochemical status of the patient. Trihexyphenidyl (6 mg per day) was used as adjuvant medication at the time of appearance of esctrapyramidal symptoms.

RESULTS

A homogenous sample of 80 schizophrenic patients were screened . Forty four subjects fulfilled the criteria and were included in the study. They were randomly assigned to the two treatment groups of centbutindole and risperidone respectively i.e. 22 patient in each group. Four out of 44 patients dropped out during the study and 2 out of 44 patients were withdrawn from the study. Amongst dropped out 2 patients belong to each group while amongst terminated both the terminated patients were of centbutindole group. Finally 38 patients completed the study i.e.18 patients in centbutindole group and 20 patients in risperidone group.

The sociodemographic and clinical variables of the sample are given in (Table no.1). This shows that there was no significant difference between centbutindole and risperidone groups with respect to age, sex , marital status, onset, numbers of episodes, clinical diagnosis and duration of illness.

The onset of effect was observed in both the study drugs from 2nd week onwards in relation to PANSS factors like total PANSS score, positive syndrome scale, negative syndrome scale, general psychopathology, activation, paranoid belligerence thought disturbance, depression and anergia (Table no.2). The steady decline in scores was observed from 3rd week to 8th week of study with both drugs. In relation to thought disturbance the significant improvement was observed from 3rd week onwards with centbutindole and 4th week onwards with risperidone. The depression (4th week) and anergia (2nd week) improved earlier to risperidone than with centbutindole. But these differences were no more perceptible at 6th week onwards.

Overall improvement of individual patients was assessed on CGI scale (Table no.3) on comparing the severity of illness at beginning of study in centbutindole group 12 patients were severely ill, 5 markedly ill and one was moderately ill. While in risperidone group 8 patients were severely ill, 9 markedly ill and 3 were moderately

TABLE 1
SOCIO-DEMOGRAPHIC & CLINICAL VARIABLES OF THE STUDY

Variables	Centbutindole (n=22)	Risperidone (n=22)
Age(Mean±SD)	27.22 yrs.	30.68 yrs.
	± 8.69	±8.78
Sex(Male/Female)	15(68%):7(32%)	17(77%):5(23%)
Marital Status Married/Unmarried/Single	9(41%):11(50%):2	16(73%):6(27%):0
Onset (Insidious/Acute)	13(59%):9(41%)	16(73%):6(27%)
Episode (Ist/>1)	10(45%):12(55%)	11(50%):11(50%)
Duration (<2yrs/>=2 yrs)	9(41%):13(59%)	8(36%):14(64%)
Clinical Diagnosis (Paranoid/Non-paranoid)	10(45%):12(55%)	11(50%):11(50%)
Family H/O Schizo. (Present/Absent)	3(14%): 19(86%)	4(18%):18(82%)

ill. At the end of study i.e. 8th week global improvement was assessed and it was observed that in centbutindole group 8 patients were very much improved, another 8 much improved, one minimally improved and another one had no improvement. While in risperidone group 12 patients were very much improved, 5 much improved and 3 minimally improved.

Side effect profile of the 2 drugs has been given in Table 4. Side effect analysis revealed that there was no significant difference in the side effect profile of the 2 drugs except on the neurologic sub scale of UKU. Five (28%) patients developed dystonia in centbutindole group while only one patient (5%) developed dystonia in risperidone group.

DISCUSSION

Out of 44 patients, 4 dropped out and 2 patients were terminated from the study. There was no obvious reason for dropping out besides absconding from the wards in both groups. This may be attributed to nature of the illness and latency of antipsychotic activity of both the drugs because all the patients dropped out either in the 1st week or at the beginning of 2nd week. The reason for termination in 1 patient of centbutindole group was developement of tremor and salivation not controlled by 6mg of trihexyphenidyl and parents wish to opt out from the study. Another patient of the same group required parenteral medication to control her agitation. The inter group comparison of two drugs showed that centbutindole and risperidone have similar onset of antipsychotic action as both the drugs showed significant decrease in the total PANSS score as well as positive syndrome, negative syndrome and general psychopathology scores from 2nd week onwards. The scores in both the groups showed a steady and significant decline from 2nd to 8th weeks of study. Although there are no treatments with proven efficacy for negative symptoms (Chouinard et al .1993 Marder,1996), centbutindole and risperidone in present study have been found equieffective for negative

TABLE 2
CHANGES FROM BASE LINE IN PANSS SCORES

Item	week 0 Mean±SD	week1	week2	week4	week6	week8
Total PANSS						
CB	98.36±16.74	94.57±20.94	76.33±18.27	61.10±22.03	50.89±21.21	45.16±18.23
RS	87.81±16.92	79.31±18.48	66.2±21.69	51.60±20.2	44.80±15.34	42.25±14.88
Positive Sym						
CB	23.95±6.23	21.90±6.95	17.28±6.42	14.02±7.01	10.63±6.91	9.33±6.87
RS	20.95±4.95	18.71±4.58	16.15±5.52	10.95±4.65	10.25±6.15	10.10±6.08
Negative Sym						
CB	28.01±10.36	25.71±11.03	22.57±9.80	17.55±8.09	14.26±6.41	12.66±6.69
RS	23.95±8.97	21.02±8.80	17.48±9.51	14.00±7.74	11.05±4.43	10.75±4.56
General Psycho						
CB	46.59±9.35	44.80±9.91	36.80±9.23	31.95±11.30	26.47±9.96	23.22±10.77
RS	42.41±8.17	38.23±8.23	32.25±9.04	26.45±8.76	23.50±7.19	21.20±6.24
Paranoid belli						
CB	11.41±2.97	10.71±3.42	7.67±3.31	6.95±4.19	5.00±3.57	3.72±2.61
RS	10.09±3.70	8.77±3.39	7.50±3.63	5.00±3.08	3.55±1.50	3.80±2.11
Thought Distur						
CB	12.59±3.92	12.19±4.31	9.71±4.24	6.75±3.85	5.78±4.25	5.50±4.37
RS	10.36±3.75	9.45±3.97	8.55±3.95	5.95±2.84	6.10±4.12	6.00±3.95
Activation						
CB	6.31±2.16	5.09±2.28	4.23±2.49	3.75±1.68	3.65±1.75	3.21±0.91
RS	5.63±3.30	3.95±2.03	3.50±0.89	3.50±0.89	3.30±0.73	3.20±0.61
Anergia						
CB	13.45±3.53	13.28±4.30	11.71±4.19	9.20±3.72	8.21±3.92	7.61±3.69
RS	11.90±4.85	11.36±4.03	9.80±4.73	8.60±3.98	6.45±2.68	6.55±3.52
Depression						
CB	9.70±3.61	9.22±3.25	8.81±3.27	7.05±3.05	5.72±2.16	5.56±1.80
RS	8.41±4.02	8.28±3.12	7.15±3.03	6.60±2.46	6.50±2.35	5.39±2.35

symptoms. However, in the literature the evidence for negative symptoms improvment with risperdone (Chouinard et al.,1993,Marder,1996) is based on limited evidence and leaves them open to question. Given the fact that risperdone has fewer EPS and potentially superior antipsychotic efficacy for positive symptoms (Jalenques,I.,1995, Mc Evoy,1994), any improvement in negative symptoms that occur risperidone may be due to reduction of secondary negative symptoms (Lieberman et al.,1994). The similar explanation is possible for improvement in negative symptoms with centbutindole in the present study.

The analysis of individual factors of PANSS showed no significant difference in paranoid belligerence and activation. However, a significant difference was observed with thought disturbance, depression and anergia. The significant improvement in thought disturbance was observed from 3rf week onwards with centbutindole and 4th week onwards with risperidone. So, it appears that thought disturbance was quicker to respond with centbutindole than risperidone. The results of phase III clinical trial support the findings of present

study. On depression and anergia the onset of therapeutic effect was earlier with risperidone as compared to centbutindole. However, at the end of six week both the drugs had equivalent effect on all these factors.

TABLE 3
COMPARISON OF SEVERITY OF ILLNESS AND GLOBAL IMPROVEMENT ON CGI SCALE

Weeks		Centbutindole (N=18)		Risperidone (N=20)	
		No.	%	No.	%
	Severity of illness				
0	Severily ill	12	67	8	40
	Markedly ill	5	28	9	45
	Moderately ill	1	6	3	15
	Global Improvement				
8th	Very much improved	8	44	12	60
	Much improved	8	44	5	25
	Minimally improved	1	6	3	15
	No change	1	6	0	0

On intergroup comparison of severity of illness at beginning and global improvement at the end of study no significant difference was observed on CGI scale in two groups. Thus present study showed that centbutindole has similar global impression with risperidone on CGI scale. Phase III clinical trial also showed no significant difference between centbutindole and haloperidol on CGI scale. Results of present study are also in consonance with pervious study by Singh et al. , (1997) . On a closer look , the initial severity of the illness on CGI scale was more in centbutindole group than the risperidone group in present trial. However , final evaluation of CGI scale reveals a similar response in both drugs. This observation indicates that even severely ill patients can be treated with centbutindole.

Side effects were assessed on UKU side effects rating scale at the end of each week. In both the groups most commonly observed side effects were concentration difficulties. lassitude, sedation, dystonia, tremors, rigidity, increased salivation, weight gain, orthostatic dizziness and accommodation disturbances. Some of these symptoms like concentration difficulties, reduced sleep, inner unrest ,emotional indifference, headache present at the first evaluation (not due to drugs) were improved with centbutindole and risperidone therapy in number of patients. This could probably be explained by considering that these symptoms were present during the schizophrenic illness. This finding is supported by an Indian study(Agarwal et al.,1998). The side effect profile was comparable in the two drugs except that 5 (28%) patients experienced dystonia in centbutindole group and on other hand only 1(5%) patient in risperidone group. In our study the incidence of dystonia for risperidone and centbutindole was with the range of various studies. These studies (Stern 1979; Keeper 1983; Arana,1987) have reported appearance of dystonia in 4-94% patients on neuroleptic treatment not treated with anticholinergic agents. Previous studies with centbutindole have reported dystonia in 20% (dose upto 4 mg/day) of patients (Doonga ji et al., 1983). However, one study recently published (Singh et al., 1999) have found no incidence of dystonia. This difference can be attributed to low dose administration of centbutindole (3 mg/day) in first 2 weeks of the study.

The majority of side effects were mild to moderate in severity, manageable and could be controlled by a fixed dose of 6 mg of trihexyphenidyl except one patient in centbutindole group. When the patient developed severe neurologic side effects not responding to 6 mg of trihexyphenidyl and resulted in premature termination of the patient from the study. Majority of side effects appeared in close proximity of their standard time of appearance in both the drugs. For instance asthenia, lassitude, akathisia, orthostatic dizziness appeared at the end of first week in both of the drugs except for asthenia in risperidone group where no consistent pattern of appearance was noted. Similarly rigidity, tremors and hypersalivation were observed during second week in most of the cases in both drugs.

The new drug centbutindole shows similar onset of antipsychotic efficacy as compared to

TABLE 4
INDIVIDUAL SIDE EFFECT PROFILE OF BOTH DRUGS

Side Effects	Centbutindole (N=18) No.	%	Risperidone (N=20) No.	%
Weight gain(1-2kg/month)	14(Mean 2.3kg ±3.48)	78	9 (Mean 2.3kg±2.81)	45
Increased salivation	12	67	11	55
Tremors	6	33	9	45
Lassitude	6	33	9	45
Sedation	7	39	4	20
Concentration difficulties	7	39	6	30
Rigidity	5	28	7	35
Increased duration of sleep	8	44	6	30
Dystonia	5	28	1	5
Hypokinesia	5	28	4	20
Orthostatic dizziness	8	44	7	35
Accomodation disturbance	2	11	5	25
Constipation	4	22	3	15
Increased sweating	3	17	1	5
Inner unrest	4	22	2	10
Amenorrhea	2	11	1	5
Depression	2	11	4	20
Akathisia	2	11	2	10
Oculogyric spasms	1	6	1	5
Decreased salivation	1	6	2	10
Headache	1	6	2	10
Decreased sexual desire	1	6	1	5
Erectile dysfunction	1	6	1	5
Rash/pruritus	1	6	0	0

risperidone which is also a new atypical antipsychotic. Therefore, centbutindole could be considered treatment of schizophrenia along with atypical antipsychotic . It has shown improvement in negative symptoms essentially similar to risperidone.

Lastly , the present study has its own limitations for instance, smaller sample size and duration. More large, long term controlled studies are required to further evaluate the antipsychotic properties and long term side effects of centbutindole and also to compare with other atypical antipsychotics.

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RAMESH CHANDRA , M.D., Formerly Junior Resident, H. SINGH, Professor, P.K. DALAL, Professor, Department of Psychiaty ,C.S.M.Medical University (Upgraded K.G.Medical College) Lucknow, O.P ASTHANA,M.D.,D.C.H.,Dy.Director & Head , J.S.SRIVASTAVA,M.D.,D.M.,Scientist E-II, Division of Clinical & Experimental Medicine, Central Drug Research Institute, Lucknow.(*Department of Psychiatry, UCMS & GTB Hospital, Dilshad Garden, Shahdara,Delhi-95).*

*** Correspondence**