

A COMPARATIVE EFFICACY STUDY OF CENTBUTINDOLE AND HALOPERIDOL IN SCHIZOPHRENIA

HARJEET SINGH, J.S. SRIVASTAVA, CHARU RAGHUVANSHI
P.K. DALAL & O.P. ASTHANA

ABSTRACT

A double blind study was undertaken to compare the efficacy between centbutindole and haloperidol. A total of 44 patients suffering from schizophrenia diagnosed in accordance to ICD-10 criteria were included. They were randomly assigned into two groups receiving centbutindole (4.5 mg) or haloperidol (15 mg) in two divided doses per day for six weeks. Each patient was evaluated on Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Scale (CGI-S) and UKU side effect scale every week. Five patients (1 patient in centbutindole group, 4 patients in haloperidol group) dropped out due to various reasons. A total of 39 patients (21 patients in centbutindole group and 18 patients in haloperidol group) completed the study. The results revealed an early onset of therapeutic effect with centbutindole for both positive and negative symptoms. However, the efficacy was comparable between centbutindole and haloperidol from 3rd week onwards.

Key words : Centbutindole, schizophrenia, antipsychotic, haloperidol

Centbutindole is a new antipsychotic 2-[gamma - (P-fluorobenzoyl) propyl]- 1,2,3,4,5,6,7, 12,12a - octahydropyrazino (2',1':6.1) pyrido (3,4-b) indole related to butyrophenone group (Saxena et al., 1973). Preclinically it has been found to have blocked amphetamine induced hyperactivity/ stereotypy and conditioned avoidance responses (Dua et al., 1974). These effects have been found in doses (on milligram basis) lower than those required for chlorpromazine and haloperidol. The drug is a dopamine antagonist but it also affects 5-HT₂ receptors (Gulati, 1990). The l-isomer of centbutindole is more active than the d-isomer (Singh et al., 1977). Clinically the drug has gone through Phase I, II and III clinical trials successfully and it has shown effective antipsychotic activity in schizophrenic patients (Doongaji et al., 1983). The pharmacokinetic study in normal volunteers has shown that peak serum levels of centbutindole were reached at 4 hours and the plasma half life was 12 hours (Paliwal et al., 1992). However it

does not produce striatal dopaminergic supersensitivity and therefore seems to have lesser potential to induce tardive dyskinesia on prolonged administration (Gulati et al., 1988). This communication reports the comparative clinical evaluation of centbutindole and haloperidol in patients of schizophrenia.

MATERIAL AND METHOD

The design of study was a double blind parallel trial comparing centbutindole with haloperidol. The subjects were schizophrenic patients diagnosed according to ICD-10 criteria. Patients satisfying both the inclusion and exclusion criteria were admitted in the hospital. They were randomised according to a pre-determined schedule to receive either haloperidol or centbutindole for a period of 6 weeks. Adult patients of schizophrenia, having no prior drug treatment for 4 weeks or drug naive before inclusion, willing to accept oral

medication, between the age of 18 to 50 years were included in the trial. Patients with hypersensitivity to drug treatment, pregnancy or lactation, co-existing severe organic diseases, malignancy, depression, drug abuse, mental subnormality and patients requiring parenteral drug or ECT were excluded from the trial. Each patient/guardian executed informed written consent before inclusion in the study. These patients were subjected to a thorough clinical examination, haematological (haemoglobin, total leucocyte count, differential leucocyte count, erythrocyte sedimentation rate) and biochemical (serum bilirubin, SGOT, SGPT, alkaline phosphatase, blood sugar and blood urea) investigations. Each patient was then randomized to receive either centbutindole or haloperidol. The drug was formulated in capsules identical in colour, shape and size. Each capsule contained centbutindole (1.5 mg) or haloperidol (5 mg) and the maximum dose was 4.5 mg and 15 mg for centbutindole and haloperidol respectively. The total duration of the study was six weeks. During this study each patient was evaluated on Positive and Negative Syndrome Scale (PANSS) by Kay *et al.* (1987), UKU Side Effect Rating Scale by Lingjaerde *et al.* (1987) and Clinical Global Impression Scale (CGI-S) every week. Initially each patient received one capsule twice a day for first two weeks. At 3rd week if the PANSS was 50% or more no escalation in dose was made, on the other hand if PANSS score was <50%, the dose of the drug was escalated from .1 BD/day to 1 TDS/day. Trihexiphenidyl was added at the time of appearance of extrapyramidal side effects. The Data was analysed using 't' test for pre and post drug.

RESULT

A total of 44 patients of schizophrenia were included in the study. They were randomly assigned to two groups namely centbutindole and haloperidol respectively containing 22 patients in each group. Five out of 44 patients dropped out during the study, its groupwise distribution being 4 (9%) out of 22 patients in haloperidol group and 1(2%) out of 22 patients in centbutindole group. So finally 39 patients completed the study, 21 patients in centbutindole

group and 18 patients in haloperidol group. The dosage of centbutindole or haloperidol was escalated from 1 capsule B.D. to 1 capsule T.D.S. in third week as in none of the cases PANSS score decreased by 50% till that time.

The sociodemographic & clinical variables of the sample are given in table 1. This shows that there was no significant difference between centbutindole and haloperidol groups with respect to age, sex, domicile, onset, duration and number of episodes. In both positive and negative syndrome with centbutindole onset of effect was observed in the first and the second week but in the haloperidol group no significant decrease was observed (Table 2 & 3). A steady decline in scores was observed from 3-6 weeks with both the drugs but no significant differences was found between the two drugs. All the 4 individual factors namely thought disorganisation, activation, anergy and paranoid showed significant decrease from their

TABLE 1
SOCIO-DEMOGRAPHIC AND CLINICAL
VARIABLES OF THE SAMPLE

Variables	Centbutindole (n=22)	Haloperidol (n=22)
Age	Mean=29.55 years SD=±8.44	Mean=30.05 yrs. SD=±9.46
Sex (M/F)	13(59%): 9(41%)	13(59%):9(41%)
M.Status(M/S/W)	14(64%): 8(36%)	14(64%):7(32%)
Onset	21(95%): 1(5%)	21(95%):1(5%)
Ins./Act.		
Episode	21(95%): 1(5%)	22(100%):0(0%)
1st/>1		
Duration	6(27%): 16(73%)	11(50%):11(50%)
<1/>1 year		
Family History of Schizophrenia Present/Absent	3(14%): 19(86%)	1(5%):21(95%)

TABLE 2
CHANGE IN BASELINE SCORE IN PANSS
SCALE ON POSITIVE SYNDROME

Weeks	Centbutindole			Haloperidol		
	n	Mean±SD	t value	n	Mean±SD	t value
0	22	27.24±5.67		22	22.82±7.85	
1	21	25.24±5.90	2.39*	22	21.91±7.03	0.76
2	21	22.26±5.49	4.33***	22	20.09±6.00	1.91
3	21	20.57±5.44	5.44***	18	18.50±4.77	4.33***
4	21	16.48±5.56	9.19***	18	15.72±4.97	7.16***
5	21	13.10±5.17	9.33***	18	12.28±4.60	9.71***
6	21	11.29±5.25	9.46***	18	11.83±4.30	10.65***

*p<0.05, *** p<0.001

STUDY OF CENTBUTINDOLE AND HALOPERIDOL IN SCHIZOPHRENIA

TABLE 3
CHANGE IN BASELINE SCORE IN PANSS
ON NEGATIVE SYNDROME

Weeks	Centbutindole			Haloperidol		
	n	Mean±SD	t value	n	Mean±SD	t value
0	22	19.56±10.07		22	21.68±10.28	
1	21	17.76±10.35	2.22*	22	20.86±09.65	1.08
2	21	16.19±09.76	5.96***	22	19.82±09.96	1.80
3	21	15.38±09.73	4.93***	18	18.22±08.33	2.57*
4	21	13.86±09.86	5.27***	18	16.17±08.99	3.29**
5	21	12.86±09.04	5.72***	18	14.61±08.78	4.38***
6	21	12.38±08.77	5.95***	18	14.17±08.25	3.98***

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

baseline scores at different points of time in the study but nowhere did the drugs differ significantly. However, in general psychopathology subscale both the drugs showed the significant decrease from the first week. The side effect analysis revealed that on psychic subscale 8 patients of the haloperidol group complained of inner unrest while only 4 patients on centbutindole complained of inner unrest. In the neurological subscale 2 patients each developed akathisia and dystonia in haloperidol group while no patient developed these side effects in centbutindole group. The individual side effect profile of both drugs has been shown in table 4. The trihexiphenidyl (6 mg/day) was added in three divided doses at the time of appearance of side effects and continued in these cases upto the end of study.

In the CGI scale, out of the 18 patients in haloperidol group, at the beginning of trial 2 patients were severely ill, 8 patients were markedly ill and 8 patients were moderately ill. At the end of trial, 2 patients were 'very much improved', 8 patients were 'much improved' and 8 patients were 'minimally improved'. In the centbutindole group, out of the total 21 patients, at the beginning of trial 2 patients were severely ill, 15 patients were markedly ill and 4 patients were moderately ill. At the end of trial of 8 patients were 'very much improved', 8 patients 'much improved' and 5 patients were 'minimally improved'.

DISCUSSION

Centbutindole is a new antipsychotic developed by Central Drug Research Institute,

TABLE 4
INDIVIDUAL SIDE EFFECT PROFILE OF
BOTH DRUGS

Side Effects	Centbutindole (n=22)	Haloperidol (n=22)
Psychic		
* Concentration Difficulties	15	15
* Asthenia/Fatigue	10	08
* Sleepiness/Sedation	10	08
* Tension/Inner Uprest	04	08
* Increased Duration of Sleep	10	08
* Decreased Duration of Sleep	03	02
* Increased Dream Activity	08	04
Neurologic		
* Dystonia	00	02
* Rigidity	11	14
* Tremor	18	16
* Akathisia	00	02
Autonomic		
* Increased Salivation	18	18
* Constipation	10	08
* Increased Tendency of Sweating	04	08
* Palpitation/Tachycardia	00	02

Lucknow. In this study centbutindole was compared with haloperidol using double blind parallel design. Out of 44 patients included in the trial 5 patients dropped out - 1 patient belonged to centbutindole group and 4 patients received haloperidol giving drop out rates of 2% and 9% respectively. A closer look at the reasons of drop out showed that in haloperidol group - 2 patients were withdrawn in the first two weeks and had to be given parenteral medication and electroconvulsive therapy. Thus the drop out in the two patients was due to inability of the drug to control the symptom in first two weeks. Remaining 2 patients opted out due to development of dystonia with haloperidol.

The intergroup comparison showed centbutindole to have an earlier onset of action as it showed significant decrease in PANSS scores in first week while haloperidol did not show a significant decrease in the scores from baseline. However there was no significant difference between two drugs from third week onwards. The decrease in positive and negative symptoms was also similar in two groups. However, our study showed that centbutindole

had better results than haloperidol on the basis of clinical global impression scale.

Thus after evaluating the findings of the present study it can be stated that this study was a comprehensive one with a 6 week duration. The standard diagnostic criteria were adhered to while selecting the sample. Double blind design was consistently maintained. The new drug centbutindole shows an earlier onset of action of anti-psychotic activity than with haloperidol. However no difference was observed between the drugs third week onwards.

There is a clear need for novel antipsychotic medications that will treat a broader spectrum of symptoms beyond the typical drugs and do so with less potential for troublesome side effects (Goff & Shader, 1995). Centbutindole is a new anti-psychotic with different pharmacological profile. This pharmacological profile is closer to the atypical antipsychotics recently coming into the market. Centbutindole has shown an earlier onset of therapeutic effects with lesser potential to induce tardive dyskinesia on prolonged administration.

REFERENCES

- Doongaji, D.R., Sheth, A.S., Paul, T., Parikh, R.M., Vahora, S.A., Apte, J.S., Desai, A.K., Upadhyay, A.K. & Satoskar, R.S. (1983) Clinical evaluation of centbutindole as an antipsychotic agent. *Indian Journal of Medical Research*, 78, 126-133.
- Dua, P.R., Dhawan, B.N., Saxena, A.K., Jain, P.C. & Anand, N. (1974) Tranquillising activity of 2-gama-(p-fluorobenzoylpropyl) - 1,2,3,4,6,7,12, 12a-octahydropyrazino (2',1':6,1) pyrido (3,4b) indole (centbutindole). *Indian Journal of Pharmacology*, 6, 5.
- Goff, D.C. & Shader, R.I. (1995) Non neurological side effects of antipsychotic agents. In: *Schizophrenia*, (Eds.) Hirsch, S.R. & Weinberger, D.R. London: Blackwell Science, 566-578.
- Gulati, A. & Bhargava, H.N. (1990) Effect of melanotropin release inhibiting factor on changes by haloperidol and centbutindole in cerebral cortical 5-hydroxy tryptamine receptors. *Pharmacology*, 41 C 21, 98-106.
- Gulati, A., Srimal, R.C. & Dhawan, B.N. (1988) Differential alteration in striatal dopaminergic and cortical serotonergic receptors induced by repeated administration of haloperidol or centbutindole in rats. *Pharmacology*, 36, 6, 396-404.
- Kay, S.R., Opler, L.A. & Lindenmayer, J.P. (1987) Reliability and validity of the Positive and Negative Syndrome Scale for Schizophrenia. *Psychiatry Research*, 23, 99-100.
- Lingjaerde, O., Ahlfors, U.G., Bech, P., Deneker, S.I. & Elegen, K. (1987) The UKU side effect rating scale. A new comprehensive rating scale for Psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatrica Scandinavica*, 76 (suppl.), 334-339.
- Paliwal, J.K., Gupta, R.C., Groner, P.K., Asthana, O.P. & Nityanand, S. (1992) Single oral dose pharmacokinetics of centbutindole, a new neuroleptic agent in healthy human volunteers. *Drug Investigation*, 4, 3, 246-251.
- Saxena, A.K., Jain, P.C. & Anand, N. (1973) Agents acting on the CNS-15; 2 substituted 1,2,3,4,6,7,12,12a- octahydropyrazino (2',1' : 6,1) pyrido (3,4-b) indoles. *Journal of Medicinal Chemistry*, 16, 560-562.
- Singh, H.K., Srimal, R.C., Raghunath, R., Jain, P.C., Saxena, A.K. & Dhawan, B.N. (1997) Evidence for stereospecific nature of neuroleptic action of centbutindole. *Indian Journal of Pharmacology*, 9, 108.

HARJEET SINGH*, MD, Professor, Department of Psychiatry, K.G.'s Medical College, J.S. SRIVASTAVA, MD, DM, Scientist, Division of Clinical & Experimental Medicine, C.D.R.I., CHARU RAGHUVANSHI, MBBS, P.K. DALAL, MD, Professor, Department of Psychiatry, K.G.'s Medical College & O.P. ASTHANA, MD, D.Ch, Head, Division of Clinical & Experimental Medicine, C.D.R.I., Lucknow.

* Correspondence