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OPEN DRUG TRIAL WITH HALOPERIDOL DECANOATE INJECTIONS IN SCHIZOPHRENIA

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SUMMARY

The present study reports results pertaining to an "open trial" with long acting haloperidol decanoate injections in the maintenance therapy of schizophrenic patients satisfying DSM-III criteria. 33 patients suffering from schizophrenia entered the trial and were put on long acting haloperidol decanoate injections. The follow-up period was 6 months and the condition of the patients was monitored every 4 weeks. 30 patients completed the trial. The results of study indicate haloperidol decanoate to be an effective agent in the maintenance therapy of ambulatory schizophrenic patients. During the period of follow-up significant reduction in manifest psychopathology was observed. Most of the patients were better off at the end of the trial. None of the patients showed deterioration during the study period. Side effects were few, the number of patients experiencing them was small and these side effects improved with passage of time.

Maintenance drug therapy is an important aspect of the treatment programme of patients with schizophrenia. It has been reported by Richards et al. (1982) that a substantial number of schizophrenic patients are either irregular in taking prescribed medication or discontinue therapy of their own accord. In this respect, availability of long acting or depot preparations of antipsychotics offer considerable advantages.

Haloperidol is one of the most widely prescribed, highly effective and well established antipsychotics (Freyhan, 1980; Ayd, 1978). Introduction of Haloperidol decanoate, which is a long acting depot neuroleptic, has added a new dimension to the maintenance therapy of schizophrenic disorders. Efficacy and safety of haloperidol decanoate has been documented in many studies (Arap Mengech & Wazome, 1984; Youssef, 1982; Roose, 1982; Richards et al., 1982; Gelder et al., 1982; Zissis et al., 1982).

The drug trial was undertaken with the aims of assessing the efficacy and safety of haloperidol in the maintenance drug therapy of ambulatory/non-hospitalized schizophrenic patients.

Material and Methods

The study was conducted at the Department of Psychiatry, Postgraduate Institute of Medical Education & Research, Chandigarh. The Department of Psychiatry runs an active outpatient clinic and also has a 24 bedded acute admission unit. The department does not have any chronic or long stay psychiatric beds.

Selection Criteria

Ambulatory schizophrenic patients of either sex receiving maintenance therapy from the outpatient clinic of the department were screened. Patients who satisfied DSM-III (APA, 1980) criteria for the diagnosis of schizophrenia and who were receiving maintenace therapy either in the form of depot preparation of fluphenazine decanoate or oral neuroleptics were taken up for the study. Patients

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below the age of 16 years or above the age of 55 years were excluded. Acutely disturbed patients who were otherwise not on maintenance drug therapy were also excluded. Pregnant women and patients with gross neurological or major physical disorders were also excluded.

Assessments

At the commencement of the study, patients were interviewed using a structured clinical interview schedule. On the basis of the clinical interview, the patients were rated on the following :

(a) The Brief Psychiatric Rating Scale-BPRS (Overall & Gorham, 1962).

(b) The Scale for the Assessment of Negative Symptoms-SANS (Andreasen, 1984).

(c) Clinical Global Impression Scale.

An eighteen item version of BPRS (Overall & Gorham, 1962) was used to obtain ratings on manifest psychopathology. SANS (Andreasen, 1984) was employed to assess the severity of negative symptoms. This scale is divided into 5 subsections : affective flattening, alogia, avolition-apathy, anhedonia-asociality and attentional impairment. The severity of the illness and improvement during the period of drug trial was assessed on clinical global impressior scale.

In addition to these instruments which assessed clinical status of the patients, following scales were used to monitor unwarranted side effects attributable to the drug therapy :

(a) Abnormal Involuntary Movement Scale (Guy, 1976).

(b) Dosage Record and Treatment Emergent Symptom Scale (DOTES).

(c) Extrapyramidal Symptom Rating Scale.

Assessment and Drug Dosage Schedule;

For maintenance therapy, haloperidol decanoate injections were administered as follows :

depending on the severity of manifest psychopathology, the patients were labelled as having mild, moderate or severe psychopathology.

For mild symptology, the patients were given 50-100 mg of haloperidol decanoate at 4 weekly interval. For moderate severity of psychopathology, patients were given 150-200 mg haloperidol once every 4 weeks and for severe psychopathology, haloperidol decanoate in the dose range of 250-300 mg at 4 weekly interval was prescribed.

Since at the commencement of the study, all of the patients were receiving maintenance drug therapy (other than haloperidol decanoate), the daily dose of existing neuroleptic was converted to mg. equivalent dose of haloperidol decanoate injections. Injections of haloperidol decanoate were administered through intramuscular route once every 4 weeks. The patients were maintained on these injections for 24 weeks. Benzodiazepines for night sedation were prescribed as and when necessary. For extrapyramidal side effects, Benzhexol in appropriate doses was also prescribed.

During the period of follow-up, the patients were reassessed on the assessment scales mentioned earlier. After the commencement of long acting haloperidol decanoate, the first two assessments were carried out at 2 weeks interval. After that, the patients were assessed once every 4 weeks. Thus every patients was assessed on 8 occasions at week 0, 2,4,8, 12,16,20 and 24.

Routine urine analysis was performed at the beginning and the end of the trial. Complete haemogramme, serum creatine, bilirubin and cholesterol estimations were also done at the start and end of the trial period.

Informed consent was obtained from each patient and /or a key relative looking after the patient before including any patient in the trial.

For data analysis paired 't' test was employed.

Results

33 patients who satisfied DSM-III (APA, 1980) criteria for the diagnosis of schizophrenia entered the trial. All these patients were receiving maintenance drug therapy from the outpatient clinic. 3 patients discontinued the treatment and did not come for follow-up assessments. 30 patients were maintained on injections of haloperidol decanoate and completed the trial period of 24 weeks.

The study sample consisted of 15 males and 15 females. The mean age of the entire cohort was 30.6 years (SD 7.66 years) and the age range was from 17 years to 50 years.

Subtyping of schizophrenia according to DSM-III was done and 11 patients were subtyped as paranoid, 13 as undifferentiated and 6 as residual subtype. As regards the duration of illness prior to inclusion in the study, 9 patients had been ill for 3 years, 5 had been ill for 4 to 5 years, 10 for 6-10 years and 6 patients had been ill for more than 10 years.

All of the trial entrants were on neuroleptic medication. 16 patients were doing well on treatment but 14 were not maintaining a satisfactory level of functioning. 21 patients were also receiving a benzodiazepine preparation and 25 patients were on antiparkinsonian agent.

Laboratory findings like total haemogramme, urine analysis, serum bilirubin, serum cholesterol, serum creatinine and random blood sugar were within normal range for trial entrants at the start as well as at the end of the trial.

Severity of the illness on clinical examination was assessed at the time of intake and was repeatedly reassessed during the priod of follow-up. For the entire cohort, the mean score on severity of illness at the time of intake was 4.35 (S.D.=0.60) which came down to 3.63 (S.D.=0.71) at the time of the final assessment at 24th week. On applying paired 't' test, this change was found to be significant ($t=5.86$, $p<0.001$). Significant reduction in the severity of illness score was first observed at 8th week and this trend was maintained all through the trial period. These findings are displayed in table 1. These results suggests that long acting injection of haloperidol decanoate is effective in the maintenance therapy of ambulatory schizophrenic patients.

As regards global clinical improvement, 2 weeks after the commencement of the trial i.e. 2 weeks after the first injection of haloperidol decanoate, 13 patients were assessed to have minimal improvement, 12 patients did not display any change and 5 patients could not be assessed. By the 4th week, global improvement was in evidence and this trend continued all through the trial period. At the end of the study period, 20 patients had shown much improvement and 10 had minimally improved. It is noteworthy that none of the patients displayed deterioration while on maintenance therapy with haloperidol decanoate injection. Because of small number of patients in each categoty, non-parametric statistical test of significance were not applied. However, paired 't' test was utilized to assess statistical significance of the difference between mean global improvement score at week 2 with that of subsequent weeks and at week 24. These comparisons brought out significant differences indicating global improvement at the end of the trial. These results are shown in Table 1.

Marifest psychopathology was assessed by employing the Brief Psychiatric Rating Scale-BPRS (Overall & Gorham,

Table 1. *Severity of illness & global improvement over the period of follow-up*

Variable	Scores at week								't' ratio of change score (paired t test)						
	0	2	4	8	12	16	20	24	0—2	0—4	0—8	0—12	0—12	0—16	0—14
Severity of illness															
Mean	4.35	4.24	4.23	4.06	4.90	3.72	3.89	3.63	1.48	1.71	3.56**	2.87**	4.79***	4.26***	5.80***
S.D.	0.60	0.59	0.50	0.57	0.59	0.61	0.73	0.71							
Improvement															
Mean	—	3.48	3.20	2.54	2.51	2.48	2.39	2.73	—	2.76*	6.07***	6.67***	4.17***	8.00***	9.27***
S.D.	—	0.50	0.71	0.76	0.72	0.82	0.56	0.47							

*p<0.05, **p<0.1, ***p<0.001

Table 2. *BPRS score over the period of follow-up*

	Score at week								't' ratio of change score '(paired test)						
	0	2	4	8	12	16	20	24	0—2	0—4	0—12	0—12	0—16	0—20	0—24
Mean	35.45	32.40	32.33	29.96	29.29	27.44	27.85	26.43	4.87	4.56	5.32	6.26	7.28	8.11	9.36
S.D.	6.61	5.60	6.57	6.95	6.38	5.00	5.50	5.28							

All 't' ratios significant at p<0.001

Table 4. *Composite side effects score over the period of follow-up*[1]

	Score at week							't' ratios at change scores					
	2	4	8	12	16	20	24	2—4	2—8	2—12	2—16	2—20	2—24
Mean	3.92	3.13	2.45	2.45	1.88	2.28	2.10	1.64	3.05**	1.43	4.63***	1.94	2.59*
S.D.	2.28	1.88	1.74	2.68	1.05	1.78	1.62						

1. paired 't' test, *p<0.05, **p<0.05, ***p<.001

Table 3. *Ratings on SANS over the follow-up period*[1]

Variable	Scores at week								't' ratios of change scores						
	0	2	4	8	12	16	20	24	0—2	0—4	0—8	0—12	0—16	0—20	0—24
Total SANS Score :															
Mean	57.58	55.92	48.0	43.63	41.72	42.80	41.60	40.10	2.96**	4.17***	5.92***	6.36***	6.02***	5.54***	5.14***
S.D.	16.37	18.49	17.57	15.56	13.44	14.86	15.89	16.68							
Affective Flattening:															
Mean	18.48	18.04	14.65	13.60	13.51	13.04	12.60	12.26	2.50*	4.10***	5.17***	5.04***	4.58***	4.40***	4.53***
S.D.	7.32	7.73	7.37	7.51	5.50	5.97	6.82	6.48							
Alogia:															
Mean	8.61	8.88	6.96	5.43	5.58	6.52	6.00	6.20	1.06	1.95	4.64***	4.93***	3.83***	3.64**	3.26**
S.D.	4.96	5.01	4.60	4.98	4.30	4.01	4.67	4.43							
Avolition:															
Mean	9.70	8.96	7.75	7.03	6.96	7.69	7.78	7.04	3.04	3.51**	5.01***	5.06***	3.57**	3.20**	4.16***
S.D.	2.71	3.14	3.42	3.45	3.10	3.49	3.13	3.21							
Anhedonia :															
Mean	14.87	13.96	13.37	12.37	11.41	12.04	12.00	11.00	3.52**	2.54*	4.44***	5.78***	5.56***	4.51***	6.38***
S.D.	3.40	3.56	3.93	3.15	2.87	2.88	3.05	3.37							
Attention :															
Mean	5.90	6.08	5.24	4.86	3.64	3.72	3.10	3.30	0.35	1.49	3.72***	4.85***	4.52***	5.94***	7.67***
S.D.	1.85	2.43	2.02	1.79	2.24	1.74	1.68	1.96							

1. Paired 't' test. *$p<0.05$, **$p<0.01$, ***$p<0.001$

1962). The mean BPRS score for the entire cohort at the time of intake was 35.45 (S.D.=6.61). This gradually declined over the study period and by the time of final assessmert at 24th week it was found to be 26.43 (S.D.=5.28). This indicates significant reduction (paired 't' test, t=9.36, p<0.001). It is worth emphasisirg that significant reduction in mean BPRS score was observed at 2nd week and this reduction continued all through the trial period (Table 2).

The effect of haloperidol decanoate on "negative symptoms" as assessed on the Scale for the Assessment of Negative Symptoms—SANS (Andreasen, 1984) was also evaluated. These results are depicted in table 3. It can be seen that haloperidol decanoate brought about significant reduction in total SANS score (of mean SANS score 57.78, S.D.=16.37 at intake with mean SANS score of 40.10, S.D.=16.68 at the termination of trial; t=5.14, p<0.001). Haloperidol decanoate was also observed to exert ameliorating effect on negative symptoms complexes of affective flattening, avolition-apathy and anhedonia (Table 3).

Through out the duration of follow-up, side effects were closely monitored. As stated earlier, to achieve this objective, 3 different kinds of instruments were used namely the Abnormal Movement Scale, Extrapyramidal Symptom Rating Scale and the Dosage Record and Treatment Emergent Symptoms Scale. On the basis of assessments on all these three scales, a composite rating of side effects was attempted and the patients were assigned to any one of the following categories : (i) no significant side effects, (ii) side effects present but do not significantly interfere with the functioning of the patients (iii) significant impairment in the functioning of the patients due to side effects and (iv) side effects nullify therapeutic effects.

15 patients were rated to have abnormal involuntary movements on AIMS (Guy, 1976) at the commencement of the trial and these were observed to persist all through the period of the trial. However, in none of the patients they were thought to outweigh therapeutic effects of haloperidol decanoate. Also, these abnormal movements were not perceived by the patients to cause significant impairment in their functioning. If anything, the mean composite side effects score gradually declined over the duration of the trial and was observed to have come down from an initial score of 3.92 (S.D.=2.28) to 2.10 (S.D.=1.62) (t=2.59, p<0.05). This result is shown in table 4.

The global assessment of parkinsonian side effects on Extrapyramidal Symptom Rating Scale also remained unchanged through out the duration of the trial period (mean rating of 1.08 (S.D.=0.64) at 2rd week and 0.94 (S.D.=0.25) at 24th week, (t=1.13, p<0.05). 3 patients had akathesia of mild nature which was transient. 6 patients had tremors of mild nature and two patients developed tremors during the period of trial. However, in none of the patients, tremors interefered significantly with their functioning. 4 patients displayed rigidity at the commencement of the trial and in 7 patients rigidity emerged as a new symptom during the trial. Lack of facial expression was common which 22 patients had to begin with and 3 patients were added to this number as they had developed this symptom later on. Rest of the extrapyramidal symptoms were uncommon.

Discussion

This open drug trial with haloperidol decanoate, though compromized to a certain extent because of short duration of follow-up and small size of the sample, nonetheless demonstrates that long acting injection of haloperidol is

an efficient agent in the maintenance therapy of ambulatory schizophrenics. The study also shows that nearly all of the patients included in the trial were doing reasonably well on intra-muscular haloperidol decanoate administered once every 4 weeks. More significantly, not even a single patient deteriorated during the period of follow-up whilst on haloperidol decanoate. It is also apparent from the present study that haloperidol decanoate can be successfully used as a maintenance agent for patients maintained on other neuroleptic medication. In this respect our findings are in agreement with the findings of Richards et al. (1982), Gelders et al. (1982), Youssef (1982) and Roose (1983).

In our study, haloperidol decanoate was found to be safe as far as production of side effects is concerned. Side effects emerging during the treatment were few and transient. Serious side effects were not encountered. Thus, it would appear that the long acting injections of haloperidol were well tolerated.

An additional advantage of haloperidol injection would appear to be its ability to combat "negative symptoms." Other drug trials with this preparation are somewhat silent on this point but results of the present work, where an established scale for the assessment of negative symptoms was employed, show that haloperidol decanoate leads to substantial improvement in negative symptoms.

To conclude, it can be summarized that introduction of haloperidol decanoate is a significant and beneficial addition to existing modalities of treatment for maintenance therapy of schizophrenia.

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REFERENCES

APA : American Psychiatric Association (1980). Diagnostic and Statistical Manual of Mental Disorders. 3rd edition, Washington, D. C. : American Psychiatric Association.

Andreasen, N. C. (1984). The Scale for the Assessment of Negative Symptoms (SANS). Iowa City : University of Iowa.

Arap Mengech, H. N. K. and Waziome, E. G. M. (1984). Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. East African Medical Journal, 61, 435-438.

Ayd, F. J. (1978). Haloperidol : twenty years clinical experience. Journal of Clinical Psychiatry, 39, 807-814.

Freyhar, F. A. (1980). Twenty years haloperidol : Clinical effectiveness and theoretical implications. Comprehensive Psychiatry, 21, 251-257.

Gelders, Y. G., Reyntjens, A. J. M., Ash, C. W. and Aerts, T. J. L. (1982). 12 months study of haloperidol decanoate in chronic schizophrenic patients. International Pharmacopsychiatry, 17, 247-254.

Guy, W. (1976). ECDEU Assessment manual for psychopharmacology. Rockville : National Institute for Mental Health, US Department of Health, Education and Welfare.

Overall, G. E. and Gorham, D. R. (1962). Brief Psychiatric Rating Scale. Psychological Reports, 10, 799-812.

Richards, S. M., Actis Dato, A. G., Zelaschi, N. M., Balbo, E. A. and Canero, E. C. (1982). Monthly haloperidol decanoate substitutes for daily neuroleptics in psychotic impatients. Current Therapeutic Research, 32, 586-589.

Roose, K. (1982). Haloperidol decanoate as a replacement for maintenance therapy with intramuscular fluphenazine decanoate in schizophrenia and other chronic psychoses. Acta Psychiatrica Belgica, 82, 216-223.

Youssef, H. A. (1982). One year study of haloperidol decanoate in schizophrenic patients. Current Therapeutic Research, 31, 976-981.

Zissis, N. P., Psaras, M. and Lykotsos, G. (1982). Haloperidol decanoate, a new long actiing antipsychotic in chronic schizophrenics : Dobuble blind comparison with placebo. Current Therapeutic Research, 31 : 650-655.