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TREATMENT OF ACUTE AND TRANSIENT PSYCHOTIC DISORDERS WITH LOW AND HIGH DOSES OF ORAL HALOPERIDOL

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ABSTRACT

The apparent rationale for the popular use of high doses of neuroleptics in psychotic patients is to increase the degree and speed of therapeutic response .However, several recent reports have questioned these claims. The present study was undertaken with the aim to compare the efficacy of high and low oral doses of haloperidol in the treatment of acute and transient psychotic disorders. The sample comprised of forty patients of both sexes diagnosed as acute and transient psychotic disorder who were randomly assigned to high dose (20 mg/day) and low dose (5 mg /day) haloperidol groups with equal number of subjects (n=20) in both groups. Weekly assessment was done on Brief Psychiatric Rating Scale and Haloperidol Side-effects Check List (day 7, 14, 21, 28, 35 & 42). Both groups showed significant improvement in BPRS from baseline scores on all assessments. Comparison of the improvement rate in both study groups revealed no significant difference.

Key Words :Oral haloperidol, low dose, high dose, acute and transient psychotic disorders

Selection of the most appropriate dose of an antipsychotic agent may help to maximize clinical benefit and minimize neurological and other side effects (Baldessarini et al., 1988). The apparent rationale for the popular aggressive use of high potency agents in high doses is to increase the degree and speed of therapeutic response. However, there is good evidence that high doses of potent neuroleptics are not more beneficial or more rapidly effective than moderate doses (Ayd, 1955). There is also some basis to suspect that high doses can yield inferior clinical effects as well as excessive neurological side effects (Wilkens and Malitz, 1960).

Beckmann et al. (1990) have indicated that lower doses are adequate for most psychotic patients and that use of higher doses is not scientifically supported. Volavka et al. (1991) have suggested that there is an optimum range or therapeutic window for haloperidol.

It is the acutely psychotic patients who have been subjected, in the past, to receive high doses of potent neuroleptics including haloperidol for their treatment (Kinross-Wright, 1995; Danik & Goverdham, 1963; Mountain, 1963). Later, in the 1970's there were still more studies claiming success in applying high doses of potent neuroleptics for the treatment of acutely psychotic patients (Oldham & Batt, 1971; Polack & Laycob, 1971; Sangiovanni et al., 1973; Donlon & Tupin, 1974; Carter, 1977; 1978; Firling, 1978). However, recent reports have questioned these claims (Bollini et al., 1984; Baldessarini et al., 1988; Beckman & Laux 1990; Volavka, 1992).

The present work aims to compare the efficacy of high and low oral doses of haloperidol in the treatment of acute and transient psychotic disorders.

MATERIAL AND METHOD

The sample for the study was selected from the patients of acute psychotic disorder of both sexes attending the Outpatients Department of Psychiatry, King George's Medical College, Lucknow,

Subjects were diagnosed as per International Classification of Diseases-10 criteria of Acute and transient psychotic disorders (F23). The sample for the study consisted of drug-naive patients fulfilling following selection criteria.

Inclusion criteria was, age of the patients between 17 and 55 years (so as to minimise age induced variations). Exclusion criteria were, allergy or hypersentivity to haloperidol; severe medical illness - presence of any physical disorder requiring active medication especially renal, hepatic, cardio vascular and endocrinal diseases so as to reduce the chances of side effects, and drug levels could be kept more or less consistent ; drug interaction could also be avoided; pregnancy - so as to minimise chances of teratogenicity; patients having neuropsychiatric illness e.g. epilepsy were excluded to maintain the homogeneity of the sample; mental retardation;drug induced psychosis or drug dependence;bipolar disorder; schizophrenia and other psychotic disorders; any other psychiatric illness; history of receiving antipsychotic medication during the present episode.

The patients fulfilling the criteria of acute and transient psychotic disorder and selection criteria were included in the study.Informed consent was obtained from each patients' relatives. All patients were assigned to a 6 week protocol. They were administered semi-structured proforma, Brief Psychiatric Rating Scale (B.P.R.S.) and Haloperidol Side-effects Check List on day 0 for baseline assessment. Patients were then randomly assigned either to high (20mg/day) dose or low (5mg/day) dose of oral haloperidol administered in identical capsules at bed time. They were given oral trihexyphenidyl 6mg/day in divided doses and lorazepam orally upto 6mg/day, if required, which was duly recorded in each case.

Each patient was then evaluated on day 7, 14, 21, 28, 35 and 42 using the B.P.R.S.and Haloperidol Side-effects Check List.

Patients were excluded from the study during administration of protocol for the following reasons:

1. Worsening of the patient's condition so as to require alternative medication.
2. Withdrawal of consent to participate further in the trial.
3. Absconding from the hospital or leaving against medical advise.
4. Development of hypersensitivity or emergence of severeside-effects.
5. Development of an acute physical illness requiring immediate intervention.

Statistical analysis was carried out by paired 't' test.

RESULTS

47 patients were initially included in the study and were divided into high dose group (n=22) and low dose groups (n=25) by random allocation. 7 patients were dropped-out prior to completion of protocol (high dose group =2 & low dose group = 5) due to following reasons:

1. Withdrawal of consent -2 patients (1 patient from high dose group and 1 patient from low dose group).
2. Had to be given parenteral medication -3 patients due to excitement and refusal to take oral medication (all from low dose group).
3. Patient absconded during the protocol -1 patient (from low dose group).
4. Patient developed severe side effects namely rigidity, tremor and akathisia -1 patient (from high dose group).

Thus 40 patients finally completed the study (high-dose group=20 and low-dose

group=20).

The largest number of the subjects in the high dose (9, 45%) and low dose groups.(10, 50%) were in the 21-30 yrs age group. Males constituted 60% of high dose group, while the low dose had an equal representation of both the sexes. Majority of the subjects were married and educated upto high school.

Table 1 shows the clinical variables of the subjects. Duration of illness was upto 7 days in majority of the subjects. Most of the subjects had first episode and without any precipitating factor. Family history of psychosis was absent in most of the cases.

TABLE 1
CLINICAL VARIABLES

	High dose No.	%	Low dose No.	%
DURATION OF ILLNESS (in days)				
Upto 7	7	35	9	45
8-15	6	30	5	25
16-30	7	35	6	30
EPISODE				
First	15	75	14	70
Second	4	20	4	20
Third	1	5	2	10
PRECIPITITATING FACTORS				
Present	1	5	2	10
Absent	19	95	18	90
FAMILY HISTORY OF PSYCHOSIS				
Present	3	15	1	5
Absent	17	85	19	95

Table 2 shows the representation of subjects in diagnostic subcategories of acute and transient psychotic disorder according to ICD-10.

TABLE 2
DIAGNOSTIC CATEGORIES ACCORDING TO ICD -X

	High dose No.	%	Low Dose No.	%
F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia	1	5	-	-
F23.2 Acute schizophrenia like psychotic disorder	12	60	10	50
F23.8 Other acute and transient psychotic disorders	7	35	10	50

TABLE 3
COMPARISON OF CHANGE IN B.P.R.S. SCORE IN HIGH AND LOW DOSE GROUPS FROM BASELINE SCORES

	High Dose (n=20) MEAN±S.D.	't'	Low Dose(n=20) MEAN ±S.D.	't'
Baseline Score	26.95±6.3	-	24.55±3.85	-
Day 7	13.55±5.61	10.80*	12.35±3.57	15.47*
Day 14	90±6.47	12.99*	17.70±4.26	18.58*
Day 21	22.70±8.04	12.63*	20.40±3.98	22.92*
Day 28	24.30±7.57	14.36*	22.10±4.04	24.46*
Day 35	25.30±7.19	15.74*	22.55±4.12	24.47*
Day 42	25.65±7.09	16.18*	22.90±3.97	25.80*

For all values d.f. = 19, *- p<.001

Table 3 shows the comparison of change in B.P.R.S. scores from baseline scores in high and low dose group (change in B.P.R.S score at day x = Baseline score - B.P.R.S. score at day x).

The mean value of B.P.R.S. scores, using the paired t test were found to be highly significant at all stages of the study, starting from day 7 to day 42 when compared with the

baseline scores.

At day 14, 2 subjects (10%) in each group showed psychotic symptoms. From day 21 onwards no subject exhibited psychotic symptoms but had scores on other item of B.P.R.S.

TABLE 4
COMPARISON OF CHANGES IN B.P.R.S. SCORES BETWEEN HIGH AND LOW DOSE GROUPS

	High Dose (n=20) MEAN±S.D.	Low Dose (n=20) MEAN ±S.D.	't'
Baseline Score	24.55±3.85	26.95±6.83	-
Day 7	12.35±3.57	13.55±5.61	1 0.81
Day 14	17.70±4.26	18.80±6.47	0.64
Day 21	20.40±3.98	22.70±8.04	1.15
Day 28	22.10±4.04	24.30±7.57	1.15
Day 35	22.55±4.12	25.30±7.19	1.48
Day 42	22.90±3.97	25.65±7.09	1.51

For all t comparisons d.f.=38, all t values are not significant

Table 4 shows the inter-group comparison of mean changes in B.P.R.S. scores between the high and low dose groups. The difference in scores in the two groups was not found to be significant at any stage of evaluation.

At day 0, lorazepam was required in 11 (55%) subjects in high dose group while it was required in 14 (70%) subjects in low dose group (p=NS), while at day 7, it was required in 11 (55%) subjects in high dose group and in 13 (65%) subjects in low dose group (p=NS).

At day 14, lorazepam was given to 11 (55%) subjects in high dose group and 12 (60%) subjects in low dose group (p=NS). On day 21, lorazepam was used in 11 (55%) subjects in high dose group and 6 (30%) subjects in low dose group (p=NS). On day 28, 4 (20%) subjects in high dose group and 3 (15%) subjects in low dose group required it (p=NS).

On day 35, 2 (10%) subjects in the high dose group and 3 (15%) subjects in the low dose group required it (p=NS).

On day 42, 1 (5%) subject in the high dose group and 3 (15%) subjects in the low dose group required lorazepam (p=NS).

The commonest side effects in the high dose group were those of dry mouth-7 subjects (35%), and blurred vision-4 subjects (20%) on day 7 and of dry mouth -5 subjects (25%) and decreased motor activity -3 subjects (15%) on day 42.

The commonest side efffects in the low dose group were those of dry mouth-3 subjects (15%), blurred vision -2 subjects (19%) and constipation -2 subjects (10%) on day 7. On day 42 the commonest side effects in this group were those of constipation -3 subjects (15%) and blurred vision -2 subjects (10%).

DISCUSSION

The use of antipsychotics in lower doses is today an accepted practice. While just a few years ago, research in this area concentrated mainly on using high doses of antipsychotic drugs to abort psychosis i.e. rapid neuroleptization (Mountain, 1963; Polak & Laycob, 1971), today most studies are concentrating on using the minimum effective dose of neuroleptics (Volavaka, 1992).

While most drug trials on acute psychosis have been limited to time periods ranging from one hour (Gerstenzang and Krulisky, 1977) to two hours (Man & Chen, 1973; Reschke, 1974) or two days (Fitzgerald, 1969; Slotnick, 1971; Ritter et al., 1972), very few have followed-up the patient over a period (Levenson, 1976; Erickson, 1978). Thus the 6 weeks duration of this study allowed for a more prolonged and complete evaluation of the subjects.

A review of previous studies reveals high improvement rates on evaluation of subjects on a standard psychiatric rating scale in the low dose group. Fitzgerald (1969) reported improvement rate of 57% in the low dose group on evaluation of subjects after 2 days of administration of haloperidol. Ritter et al. (1972) reported improvement rate of 60% in the low dose group on evaluation after 2 days while Slotnick (1971) reported an improvement rate of 50% after 2 days in the low dose group. Man

& Chen (1973) reported an improvement rate of 23% in the low dose group at 2 hours while Anderson et al. (1976) reported an improvement rate of 50% in the low dose group at 3 hours. Levenson et al. (1976) reported an improvement rate of 75% on evaluation after 21 days in the low dose group. Gerstenzang & Krulisky (1977) in an evaluation of subjects after one hour reported an improvement rate of 50%. Erickson et al. (1978) evaluated patients in the variable dose group at time intervals of 1 day, 5 days and 18 days and reported improvement rates of 26%, 60% and 69% respectively. Neborsky et al. (1981) evaluated subjects at 4 hours, 14 hours and 7 days and reported improvement rates of 34%, 39% and 66% respectively.

Other workers such as Escobar & Barron (1983), Dubin et al. (1985), Nishikawa (1985), Neto et al. (1988), Coryell & Kelly (1990), Volavka (1992) have all reported significant improvement rates of 68%, 71%, 79%, 74%, 59% and 70 % respectively on evaluation after 7 days.

The findings of the present study are in consonance with the earlier studies. The baseline values of B.P.R.S scores in the low dose group was 26.95±6.83.The group showed highly significant ($p<.001$) improvement on day 7 with mean change of 13.55±5.61, thus showing improvement of 50.12% from baseline. The entire group then showed continuous improvement at all the following evaluations and no subjects showed a rising value of B.P.R.S. scores.

In the high dose group Fitzgerald (1969) reported an improvement rate of 48% on evaluation after 2 days. Slotnick (1971) also evaluated patients after 2 days and reported an improvement of 50%. Ritter et al. (1972) reported an improvement of 68% in the high dose group on evaluation after 2 day, while Man & Chen (1973) evaluated subjects after 2 hours and reported improvement of 22%. Anderson et al. (1976) also evaluated patients after a short duration of 3 hours and reported improvement rate of 42%. Levenson et al. (1976) evaluated subjects after a longer duration of 21 days and reported an improvement of 80%. Gerstenzang & Krulisky (1977) on evaluation of subjects after 1 hour, reported an improvement of 77% while Erickson et al. (1978) on evaluation of subjects on days 1, 5 and 18 reported improvement rates of 36%, 59% and 73% respectively. Neborsky et al. (1981) evaluated subjects after 4 hours, 14 hours and 7 days and reported improvement rates of 40%, 38% and 65% respectively.

Escobar & Barron (1983), Dubin et al. (1985), Nishikawa & Tsudo (1985), Neto et al. (1988), Coryell & Kelly (1990) and Volavka (1992) have also reported significant improvement rates of 65%, 73%, 70%, 55% and 67% respectively after 7 days in the high dose group.

In the present study too, patients in the high dose group showed highly significant improvement ($p<.001$) from the baseline at all the evaluations. The change in B.P.R.S. scores from the baseline at days 7, 14, 21, 28, 35 and 42 were 12.35±3.57 (50.30%), 17.70±4.26 (72.09%), 20.40±3.98 (84.00%), 22.10±4.04 (90.02%), 22.55±4.12 (91.85%) and 22.90±3.97 (93.28%) respectively.

The comparison of the subjects in the two groups of low and high dose of haloperidol also revealed findings similar to previous studies. These studies reported similar improvement rates in the two dosage groups with no significant difference between them, namely, Fitzgerald (1969) 57% and 48% in the low and high dosage groups, Slotnick (1971) 50% and 50%, Ritter et al. (1972) 60% and 68%, Man & Chen (1973) 23% and 22%, Anderson et al. (1976) 50% and 77%, Erickson et al. (1978) 26% and 36% on day 1, 60% and 59% on day 5 and 69% and 73% on day 18 and Neborsky et al. (1981) 39% and 40% after 4 hours, 34% and 38% after 14 hours and 66% and 65% after 7 days.

Escobar & Barron (1983), Dubin (1985), Nishikawa & Tsudo (1985), Neto et al. (1988),

Coryell and Kelly (1990) and Volavka (1992) have also reported similar improvement rates of 68% and 65%, 71% and 73%, 79% and 76%, 74% and 70%, 59% and 55%, 70% and 67% respectively in the low and high dose groups after 7 days.

From the findings of the present study, it can be concluded that the low dose of oral haloperidol is equally effective as high dose and causes lesser side effects.

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