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EFFICACY OF PROPRANOLOL ON SCHIZOPHRENIC THOUGHT DISORDER

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SUMMARY

15 schizophrenic patients were treated with dl-propranolol in a 4 week open study. Dosage was gradually increased over a period of 17 days to 1920 mg/day. Improvements were rated on Thought Disorder Scores (A & B) of the MBPRS and CPRS subscale for schizophrenia. Majority of the patients showed a 50% improvement in terms of their residual scores by the 4th week of treatment and the side effects experienced were minimal.

Clinical reports over the past decade have amply exemplified the role of beta blockers in a variety of psychiatric conditions. Promising results have been observed in psychotic conditions when beta blockers, especially propranolol is administered in high doses. The preliminary observations of Atsmon *et al.* (1970), have triggered of a series of open as well as controlled investigations into the therapeutic potential of propranolol. In a clinical trial of propranolol in 13 patients (including 9 schizophrenics) a quick symptomatic improvement was observed when doses as high as 5, 800 mg/day were used. Yorkston *et al.* (1974; 1976; 1977; 1978) investigated the antipsychotic effects of this compound in 55 schizophrenics with florid features. 28 of these lost their schizophrenic symptoms, and 17 of those who improved were on propranolol alone. When compared against placebo in 14 patients in a double blind manner (Yorkston *et al.*, 1977), the propranolol group was significantly better than placebo when the sum of the three thought disorder scales were considered after the 12th week ($p<0.035$). Improvement in the thought disorder scale continued even after the 12 week study. Although the best results have been observed in those ill for less than 1 year (Yorkston *et al.*, 1976), 15 out of 38 of this series who remitted completely were ill from 1-30 years. Patients in this series usually showed a gradual improvement, with hallucinations stopping before secondary delusions and the latter remitting more often gradually than abruptly. Worsening on withdrawal of propranolol in 20 chronic schizophrenics was observed in an unpublished study by Yorkston and colleagues, with development of thought disturbance, delusions, and abnormal activity levels. Auriol *et al.* (1972) have also reported improvement in thought disturbances in 30 psychotics on low doses of pindolol (7.5—45 mg). Lindstrom and Persson (1980) studied the effect of propranolol in 12 chronic schizophrenics (dose 1280-1920 mg/day) in a double blind study. They recorded significant improvement in the CPRS subscale of thought disturbances in 6 Patients on Propranolol within two weeks of therapy. Recently, Sheppard (1979) has reported an improvement in 7 out of 9 schizophrenics with Propranolol, with an improvement in schneiderian symptoms in 3 patients. Hirsch *et al.* (1981) have shown significant improvements in the ratings of thought disorder ($P<0.02$ and $P<0.05$) of the BPRS with d-propranolol. Improvements in thought disorder have also been found related to the dose *i.e.* the higher the dose, the lower the thought disorder score (Yorkston *et al.*, 1981).

Summarizing, in terms of therapeutic

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results, the various investigations may be divided into 2 groups : positive (Atsmon *et al.*, 1971 ; 1972 ; Volk *et al.*, 1972; Steiner *et al* ., 1973; Rackensperger *et al.*, 1976; Yorkston *et al.*, 1974; Zerssen, 1976; Yorkston *et al.*, 1976a, 1976b; Yorkston *et al.*, 1977; Ridges 1977; Elizur *et al.*, 1979; Belmaker *et al.*, 1979; Sheppard, 1979; Hanssen *et al.*, 1980 and Lindstrom and Persson, 1980) and negative studies (Stam, 1971; Gardos *et al.*, 1973; Orzak, 1977; King *et al.*, 1980; Peet *et al.*, 1981a; 1981b; Myers *et al.*, 1981). However, controlled studies have hitherto been scanty (Yorkston *et al.*, 1977; Ridges *et al.*, 1977; Elizur *et al.*, 1979; Lindstrom and Persson, 1980; King *et al.*, 1980 and Peet *et al.*, 1981a and b). Studies using drug combinations (Beta blockers and neuroleptics) are frought with the problem of attributing therapeutic superiority to a specific drug response and also the increase in plasma levels of neuroleptics due to competitive metabolism by beta blockers (Peet *et al.*, 1981b).

The present pilot investigation summarizes the effect of dl-propranolol on the thought disorder scores of 15 schizophrenic patients.

MATERIAL AND METHOD

Sample :

The investigation was conducted upon 15 male patients, who were admitted in the Department of Psychiatry, King George's Medical College, Lucknow and diagnosed as Schizophrenic psychosis by 2 psychiatrists independently on the guidelines of I.C.D. IX (1977). Their age ranged from 20 to 35 years (mean 28.4 years) and duration of illness between 3 to 24 months (mean 9.63 months). 60% of the sample had an insiduous onset of illness and 40% had a family history of schizophrenia in their first degree relatives. The diagnostic subtypes included 6 hebephrenic, 5 paranoid and 4 chronic undifferentiated schizophrenics. All were in good physical health and detailed investigations including an EKG were done in each case to exclude any case with a cardiac condition, bronchial asthma, obstructive pulmonary disease, pheochromocytoma, diabetes mellitus and an established history of alcohol or drug abuse prior to propranolol therapy. An informed consent was obtained in each case.

Design :

80 mg. dl-propranolol supplied as tablets was given orally in 4 divided doses. The dose was kept at 160 mg/day during the first 6 days and then increased gradually so as to to reach 1920 mg/day by day 17. This dose was kept constant till the end of the study (day 28). Pulse and blood pressure were closely monitored and the drug was withdrawn gradually if the pulse rate fell below 55/mt and b.p. below 80/50 mm of Hg, and the patient considered a dropout. No concommitant medication was permitted during the study period.

Assessment instruments :

The response of patients to propranolol on thought disorder was noted by the change in thought disorder (A and B) scores selected from the Modified Brief Psychiatric Rating Scale (Overall and Goreham, 1962) and the Comprehensive Psychopathological Rating Subscale for patients with schizophrenic syndromes (Jacobsson *et al.*, 1978). A Side Effects Checklist was also administed. The MBPRS was administered at Week 0, 2 and 4, while the CPRS subscale and side effects check-list at weeks 0, 1, 2, 3 and 4. The results were expressed by calculating the percentage residual scores derived from the difference between the initial and final scores on the items representing thought disorder.

RESULTS

Table-1 demonstrates the percentage residual scores in terms of improvement on the two thought disorder subscales of MBPRS. By the end of the 2nd week 20% patients had shown an improvement of 51% and more on the scores of thought disorder (A). By the end of the 4th week 73%

TABLE-I—*Percentage residual improvement on thought disorder (MBPRS)* (N=15)

From Baseline	Thought Disorder A*		Thought Disorder B**	
	Wk 2	Wk 4	Wk 2	Wk 4
Worse	0	0	0	0
Same	0	0	0	0
Improved up to 25%	3	0	4	0
,, 26—50%	9	4	9	4
,, 51—75%	2	6	2	6
,, >75%	1	5	0	5

*Thought Disorder A : Conceptual Disorganization, Hallucinatory behaviour, Unusual Thought Content.

*Thought Disorder B : Blunted Affect, Grandiosity, Suspiciousness, Emotional withdrawal, Motor Retardation, Mannerisms & Posturing.

patients had shown a similar degree of improvement on these parameters. For the scores of thought disorder (B), the number of patients who improved by more than 50% by the end of 2nd and 4th weeks were 13.3% and 73% respectively. No patient worsened or remained the same during the trial period.

Table-II demonstrates the percentage residual scores in terms of improvement on the two thought disorder scales of CPRS subscale. In terms of improvement 6.7%, 40%, 73.3% and 86.7% patients showed more than 51% improvement during the Ist, 2nd, 3rd and 4th weeks respectively on Thought Disorder (A). The corresponding percentage of patients who showed a similar degree of improvement on thought disorder (B) subscale during the 4 weeks of therapy were 0%, 20%, 60% and 86.7% respectively. 1 patient showed no change on both thought disorder subgroups even at the end of 4 weeks. However, no patient worsened while on propranolol. Duration of therapy and increasing dosage were found to be well correlated with the number of patients showing improvement.

TABLE-II—*Percentage residual improvement on thought disorder (CPRS)* (N=15)

From Baseline	Thought Disorder : A*				Thought Disorder : B**			
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4
Worse	0	0	0	0	0	0	0	0
Same	6	3	2	1	9	3	2	1
Improvement Up to 25%	4	4	1	0	2	2	2	0
Improvement Up to 26-50%	4	4	1	1	4	7	2	1
Improvement Up to 51—75%	0	3	5	2	0	2	4	3
Improvement >75%	1	3	6	11	0	1	5	10

*Thought Disorder : A—Feeling Controlled, Incoherent Speech, Hallucinations.

**Thought Disorder : B—Ideas of Persecution, Incongruence of Affect, Withdrawal, Blank spells, Slowness of Movements, Mannerisms & Posturing.

Table-III demonstrates the frequency of commonly occurring side effects. The commonest side effects were bradycardia (33.3%), fatigue (33.3%), weakness (26.7%) and abdominal pain (20.0%). Light headedness, nausea, vomiting and diarrhoea occurred infrequently (6.7%). Most of the patients experienced side effects of mild intensity but for 1 patient who had severe fatigue. There was no association between development of beta blocking effects and clinical improvement. In addition to the 15 patients included in this analysis, 3 patients developed severe bradycardia (Pulse<55/minute) and were therefore dropouts.

TABLE III—*Frequency of commonly occurring side effects*

S. no.	Side Effects	N	%
Cardiovascular :			
1.	Bradycardia	5	33.3
2.	Hypo/hypertension	..	..
3.	Cardiac Decompensation	..	..
C.N.S.			
4.	Light headedness	1	6.7
5.	Weakness	4	26.7
6.	Fatigue	5	33.3
G.I.T. :			
7.	Nausea	1	6.7
8.	Abdominal Pain ..	3	20.0
9.	Vomiting	1	6.7
10.	Diarrhoea	1	6.7
Respiratory :			
11.	Dyspnoea	..	..
12.	Rhonchi	..	..

DISCUSSION

This pilot investigation of propranolol on Indian patients suggests that the drug possesses anti-psychotic properties as observed by reduction in the scores of schizophrenic thought disorder. Improvement was witnessed sometime between the 1st and 2nd weeks of therapy at a dose between 480 mg/-day to 960 mg/day. The improvements were more remarkable at a higher dosage i.e. 1920 mg/day. In studies employing the use of propranolol in high doses such as upto 4,000-5,000 mg/day toxic effects often pose a major problem (Atsmon *et al.*, 1971; 1972; Yorkston *et al.*, 1974). In this study, a gradually increasing dosage schedule has enabled a smooth drug administration period which was free of fatal or life threatening side effects. Although bradycardia was the most frequent side effect, it was not serious enough to warrant a discontinuation of propranolol except in 3 patients. Furthermore, there was no correlation between bradycardia and hypotension with remission of schizophrenic symptoms as reported by Volk *et al.* (1972) and side effects when severe usually developed within the first 72 hours. The mean duration of illness in our sample was less than 1 year ($\bar{X}$=9.63 months) and was possibly a factor contributing to the better therapeutic outcome. Although the present study is an open trial and is subject to the error of a personal bias, even double blind studies comparing propranolol to a potent neuroleptic or placebo is subject to certain pitfalls i. e. development of beta blockade effects can distinguish the drug from placebo and extrapyramidal symptoms being conspicuously absent in this group of drugs may differentiate the drug from neuroleptics. This however, is hard to overcome. The mechanism of effect of propranolol continues to be an area of promising research and several studies involving biochemical and psychophysiological parameters are in progress. Before the results of this study can be generalized it would be essential to substantiate these results in a study using a double blind controlled design conducted on a larger sample over a longer period of time. It may be that this group of compounds might soon be added to our armamentarium for the therapy of schizophrenia as a new non-neuroleptic group of compounds. Determination of its mechanism of action might also help in our understanding of the aetiology of schizophrenia.

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