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Propranolol in Schizophrenia: A Double Blind, Placebo Controlled Trial of Propranolol as an Adjunct to Neuroleptic Medication

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Summary: A double blind, placebo controlled trial was carried out to examine the contribution of propranolol as an adjunct to neuroleptic medication in the treatment of chronic schizophrenic patients whose florid symptoms had not remitted with neuroleptic medication alone. Propranolol was shown to have a more beneficial effect than placebo, but the results were much less dramatic than those which have been described in previous studies. Recent work has shown that there may be a pharmacokinetic interaction between propranolol and neuroleptics, and this should be considered as one possible explanation of our findings.

The evidence that beta-adrenergic blockers may be of use in schizophrenia is largely drawn fron uncontrolled clinical investigations (Atsmon *et al,* 1971; Yorkston *et al,* 1974; Van Zerssen, 1976; Yorkston *et al,* 1976; Shepherd, 1979). There are two double blind, placebo controlled trials of propranolol in neuroleptic treated patients which suggest that the drug is effective. These were carried out by Yorkston and his colleagues (1977) and Lindström and Persson (1980). However the number of patients included in these trials, 14 and 12 respectively, was rather small. Myers and his colleagues (1981) also investigated the effectiveness of propranolol as an adjunct to neuroleptic medication in a double blind, controlled trial involving 20 patients but they were unable to demonstrate a beneficial effect.

Recently published double blind trials have failed to show any beneficial effect of propranolol when given alone. King (1980) compared propranolol with placebo and the results were negative. However only 5 patients were investigated, in a trial of crossover design, and each patient was treated double blind for only three weeks. Peet *et al* (1981) conducted a trial comparing propranolol with chlorpromazine, and placebo, in the treatment of 53 patients suffering from chronic schizophrenia. They were unable to find any improvement in schizophrenic symptomatology in subjects on propranolol, relative to placebo. Patients included in this study were less floridly psychotic than in previous investigations.

There are some reports of beta-adrenergic blockers acting in a contradictory way. Steinert and Pugh (1979) described two patients who developed a schizophreniform psychosis after being treated with beta-adrenergic antagonists for cardiac conditions. Similar findings have been described by Gershon *et al* (1979) and Whitlock and Bonfield (1980).

Method

The present study was of double blind, placebo controlled design. All of the subjects were in-patients and had been treated with neuroleptic medication previously. Propranolol or placebo was added to the neuroleptic medication, which the patients continued to receive. Patients had to be classified as suffering from schizophrenia by the Feighner criteria for schizophrenia (Feighner *et al,* 1972); and the diagnosis was confirmed by applying the Present State Examination (PSE) to the case notes (Wing, 1974). Patients had florid symptoms (confirmed using the Brief Psychiatric Rating Scale (BPRS)), despite current neuroleptic medication. Moreover, patients had to be in good general physical health with no evidence of any significant active cardiovascular or pulmonary disease. They did not have conditions for which propranolol is contraindicated. In particular, patients with a history of asthma or bronchitis were excluded.

Treatment schedule

Patients were treated for 12 weeks with either propranolol or placebo. Those in the active treatment group initially received 40 mg of propranolol twice a day. The dose was then increased each week, for five weeks, until patients received 320 mg twice a day. All the tablets used in the trial (of whatever strength) looked exactly the same. Every patient received two

tablets twice a day. Side effects, blood pressure, and pulse were monitored each day. If there were any problems the dose was dropped back to the previously tolerated level, or the patient was withdrawn from the study. If there was significant improvement before week 5, in the view of the psychiatrist and nursing staff, then the dose the patient was taking at the time was held until the end of the trial.

A verbal explanation was given to each patient and nearest relative, describing the purpose, nature and possible hazards of the study.

The psychiatric condition of the patients was monitored by using the Nurses Observation Scale for In-patient Evaluation (NOSIE) (Honigfeld and Klett, 1965; Honigfeld, 1973; Philip, 1979), the Modified Brief Psychiatric Rating Scale (BPRS) (Yorkston *et al*, 1977; Overall and Gorham, 1962) and the Montgomery Schizophrenic scale of the Comprehensive Psychopathological Rating Scale (CPRS) (Asberg *et al*, 1978; Montgomery and Montgomery (1980)). Analogue scales of severity of illness and global change in mental state were completed by the psychiatrist, who made the more detailed assessments, and the nursing staff. Assessments were carried out prior to treatment and after one, two and three months of treatment.

Side effects of the medication which the patients were receiving before the trial began were recorded. The principle side effects of propranolol, for example dizziness, nausea or drowsiness, were also enquired about prior to treatment to avoid these being attributed mistakenly to the drug. During the trial the presence and severity of side effects were recorded once a week.

Results

In all 41 patients were included in the trial. Twenty-one were treated with propranolol and twenty were allocated to placebo. Thirty-eight patients completed the trial. Three patients were withdrawn. One patient on propranolol was withdrawn after a physical illness which was unrelated to the trial. Another had to be withdrawn because he was transferred from one ward to another during industrial action. The third patient was withdrawn because of persistent dizziness. She was found to be in the placebo group. The age of the patients ranged from 30 to 66 years. The mean age was 44.96 years (propranolol group 44.42, placebo group 45.53). The age of onset of illness ranged from 14 to 47 years, the mean being 24.55 years. The mean length of the present admission was 15.74 years.

There was no significant difference between patients allocated to propranolol and placebo in age, age of onset, length of present admission, marital status, premorbid social adjustment, family psychiatric history, family history of schizophrenia, history of alcohol abuse prior to onset of schizophrenia, social class, education, number of admissions, and recent employment.

Dose

Significantly more patients allocated to propranolol were treated at a reduced dose. Out of the 21 patients treated with propranolol, 13 completed the trial at the full dose of 640 mg per day, 3 received 480 mg per day, and 5 received 160 mg per day. One of the patients in the placebo group had his apparent dose reduced to the equivalent of 480 mg per day; but none of the rest of this group ended the trial on the equivalent of 160 mg per day (Tau c = 0.34, $P < .005$).

Psychometric tests

In Tables I and II, the results of the special tests are shown. The statistical analysis was carried out using the change scores, i.e. the difference between the scores obtained at weeks four, eight and twelve, and the score prior to treatment. Kendall's tau (Kendall, 1962) was used because it makes no assumptions about the distribution of the data (except that they can be seen as categories ranked in order), it is appropriate for ordinal measurements, and it does not pay undue attention to outlying values. The mean values are also given for greater clarity.

It should be noted that the number of patients available for assessment varied from one week to another. In the Tables, the mean score recorded at each point is the average for all patients assessed at that time. On the other hand, the mean change has been calculated for those patients who completed the test on both occasions. For this reason, the numbers given under mean change differ slightly from the simple differences that would be obtained by subtracting one row from another in the Tables.

Results on NOSIE

There was no substantial difference in the progress of the two groups on the social interest, neatness, retardation or depression scales. On the psychoticism scale the propranolol patients tended ($P < .1$) to do better at week four. On the social competence scale there was a tendency ($P < .1$) for the outcome on propranolol to be better than that on placebo at all three follow up points. On the irritability scale there were differences in favour of propranolol at week four (Tau c = .31, $P = .042$) and at week twelve (Tau c = .41, $P = .014$). On the total NOSIE score, the differences were consistently in favour of propranolol, and achieved statistical significance at week four ($P = .048$), and week twelve ($P = .018$) (see Table I).

TABLE I

Total NOSIE scores with change scores

Week	Mean score (propranolol)	Mean score (placebo)	Mean change (propranolol)	Mean change (placebo)	Tau c	P
0	160.10	164.00	–	–	–	–
4	163.52	158.05	3.43	−5.50	.31	.048
8	166.06	164.28	6.39	−0.18	.24	.117
12	167.37	164.84	9.32	0.78	.40	.018

Low score = more disturbed. Tau c and P on change scores.

TABLE II

Montgomery Schizophrenia Scale results with change scores

Week	Mean score (propranolol)	Mean score (placebo)	Mean change (propranolol)	Mean change (placebo)	Tau c	P
0	14.05	12.68	–	–	–	–
4	12.05	13.32	2.47	−0.61	.16	.201
8	10.44	12.83	4.31	0.41	.34	.046
12	12.76	13.00	2.14	0.11	.12	.273

High score = more disturbed. Tau c and P on change scores.

Results on BPRS

Although the improvement on propranolol was usually greater than that on placebo, in no case did the difference in progress as measured by the BPRS reach statistical significance, either on the total score or on the three sub-scales.

Results on CPRS (see Table II)

No substantial differences were recorded on the depression score of the CPRS. On the Montgomery Schizophrenia Scale there were consistent differences in favour of propranolol, which were significant at week eight (P = .046).

Global scores

On psychiatrists' global scores, differences between the clinical progress of the placebo and propranolol groups were slight, whether on ratings of absolute severity of illness or of perceived change, and none of the differences approached statistical significance. Results were as meagre from the nurses' assessment of severity of illness; but on perceived changes the global rating after eight weeks tended to confirm a superior improvement by patients on propranolol (Tau c = .22, P = .07).

Side effects

Few patients included in the trial complained of side effects. Some patients suffered from poor appetite, indigestion, fatigue, insomnia, and dizziness before the trial began. There was no significant difference in the changes in side effect scores of those patients treated with propranolol or placebo for Parkinsonian symptoms, nausea, poor appetite, indigestion, fatigue, insomnia, or dizziness.

Discussion

The results of this investigation showed that propranolol was more effective than placebo. This was mainly shown by nurses' assessments on the NOSIE and a global rating scale. Improvement at eight weeks was also shown in the CPRS schizophrenia scale, as rated by a psychiatrist. However these differences were not so great as the changes which were reported by Yorkston. This may be explained by the greater chronicity of illness in the patients taking part in our study compared with Yorkston's subjects. Certainly the chronicity of illness in our patients made this a hard test for propranolol. It is also noteworthy that although patients in the propranolol group showed a significant improvement on the NOSIE after one month, the

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greatest effects of treatment were shown after three months. Thus, the beneficial effects may only become apparent after a prolonged trial of treatment. Moreover, the changes shown on the irritability sub-scale of the NOSIE suggest that propranolol may be of great help in reducing irritability in schizophrenic patients. This may prove to be of great importance, since irritability is often a major problem in the rehabilitation of patients suffering from chronic schizophrenia.

Mode of action

The mode of action of propranolol in the treatment of schizophrenia is not clear. Beta-adrenergic blockers have been shown to act centrally both in animals (Conway *et al*, 1978), and man (Gardos, 1973). But propranolol does not block dopamine receptors (Laverty and Taylor, 1968) and has no effect on plasma levels of prolactin (Shepherd, 1979; Elizure *et al*, 1978). There is evidence, however, for a stereospecific interaction of propranolol and other beta-adrenergic antagonists with 5 HT receptors (Middlemiss *et al*, 1977).

Recently a pharmacokinetic interaction between propranolol and chlorpromazine has been demonstrated (Peet *et al*, 1981). Plasma levels of chlorpromazine, total pharmacologically active neuroleptic compound in serum, and serum prolactin were markedly and significantly increased during treament with propranolol. It is not clear whether other neuroleptic drugs also show this interaction. Thus it could be that in schizophrenia propranolol acts by potentiating neuroleptics, and it may be clinically useful to raise blood levels of chlorpromazine by adding propranolol to the treatment regime.

The negative results of trials by Peet (1981) and King (1980), when propranolol was compared with placebo, makes one question whether propranolol is of benefit to schizophrenics when given alone. A comparison between our study and the two above is difficult, however, since the patients included in our investigation suffered from more florid symptoms than the other patients who were, in addition, treated for briefer periods. We note also, however, that Gruzelier *et al* (1980) have shown that normal controls and schizophrenics on propranolol, either alone or combined with neuroleptics, exhibited superior active and passive avoidance learning, compared with schizophrenic patients who were receiving conventional neuroleptic treatment.

Finally, Yorkston *et al* (1981) compared chlorpromazine with propranolol in the treatment of acute schizophrenia and were unable to find any difference in efficacy between the two treatments. Nevertheless, propranolol may be of benefit in the treatment of chronic schizophrenia and the results of our study support the need for further investigation in this area.

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