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Propranolol in Schizophrenia
I. Comparison of Propranolol, Chlorpromazine and Placebo

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Summary: Fifty-three hospitalized chronic schizophrenic patients were treated with either propranolol, chlorpromazine or placebo in a double-blind randomized trial for up to three months. Propranolol in a usual dose of 640 mg/day, produced marked cardiovascular effects but no improvement in schizophrenic symptomatology relative to placebo. The effects of chlorpromazine were small and inconsistent.

There is no doubt that chlorpromazine and related neuroleptics are effective in the treatment of acute schizophrenia and in the prevention of acute relapse in chronic schizophrenic out-patients. However, the efficacy of neuroleptics in the treatment of long-term hospitalized chronic schizophrenic patients is open to question (Hughes and Little, 1967; Letemendia and Harris, 1967; Tobias and MacDonald, 1974). This question has been highlighted by recent awareness of the long-term adverse effects of phenothiazines including tardive dyskinesia (Klawans *et al*, 1980) and possible drug-induced withdrawal psychosis (Chouinard and Jones, 1980).

Neuroleptics are thought to act by blocking postsynaptic dopamine receptors, and it is probably the resulting dopamine receptor super-sensitivity which leads to the development of tardive dyskinesia (Marsden and Jenner, 1980). Reports that propranolol may be effective in the treatment of schizophrenia have therefore aroused great interest, because propranolol does not significantly block dopamine receptors (Bremner *et al*, 1978) and does not induce tardive dyskinesia with long-term use. In addition to reducing the risk of tardive dyskinesia, a drug such as propranolol with a novel mode of action in schizophrenia could also open the way to the successful treatment of many long-stay chronic schizophrenic patients who are wholly or partly resistent to conventional neuroleptics.

Most studies of propranolol in schizophrenia have lacked a control group. Results of open studies have been equivocal. Whilst there have been some enthusiastic positive reports (Atsmon *et al*, 1972; Yorkston *et al*, 1974, 1976; Ridges *et al*, 1977; Elizur *et al*, 1979; Sheppard, 1979; Hanssen *et al*, 1980), others have found propranolol to be devoid of effect in schizophrenia (Stam, 1971; Gardos *et al*, 1973; Rackensperger *et al*, 1974; v. Zerssen, 1976; Belmaker *et al*, 1979) and there are anecdotal reports of alleged precipitation of schizophreniform symptoms by propranolol (Fraser and Carr, 1976; Koehler and Guth, 1977; Gershon *et al*, 1979; Steinert and Pugh, 1979; Whitlock and Bonfield, 1980). There have been two placebo-controlled studies in which propranolol appeared to have an anti-schizophrenic effect, but the propranolol was given in addition to existing neuroleptic treatment rather than as sole agent (Yorkston *et al*, 1977a; Lindström and Persson, 1980). We have shown that there is a pharmacokinetic interaction between propranolol and chlorpromazine, such that plasma levels of chlorpromazine and its active metabolites increase markedly when propranolol is given in addition to chlorpromazine (Peet *et al*, 1980, 1981). Therefore, studies in which propranolol is given in addition to neuroleptics cannot provide any evidence concerning the absolute efficacy of propranolol. There has been one small double-blind placebo-controlled study in which propranolol showed no advantage over placebo in the treatment of chronic schizophrenia (King *et al*, 1980). The only other controlled trial is that of Yorkston *et al* (1981) who compared propranolol and chlorpromazine in the treatment of acute schizophrenia. Although these authors concluded that the two drugs were of similar overall efficacy, there were significant differences favouring chlorpromazine over propranolol on a number of measures.

The present study is the first double-blind com-

parison of propranolol, chlorpromazine and placebo in the treatment of chronic schizophrenic in-patients.

Methods

The study was conducted to a standard protocol in four centres: Parkside Hospital, Macclesfield, Cheshire; St Edward's Hospital, Cheddleton, Leek, Staffordshire; Worcester Royal Infirmary; and Holywell Hospital, Antrim, N. Ireland. Central coordination was maintained from the Clinical Research Department of ICI Pharmaceuticals Division in order to ensure procedural compatibility between the centres. The study was approved by the Ethical Committees of the hospitals involved and written informed consent was obtained from all patients and from their nearest relatives when available.

Subjects for the study were informal in-patients with a diagnosis of chronic schizophrenia agreed upon by two independent psychiatrists and supported by application of the criteria of Feighner *et al* (1972). Patients of either sex aged under 70 years were eligible for inclusion in the trial; relevant physical illness, including heart disease, asthma, liver disease and diabetes, a history of alcoholism or drug dependence, or a medical need for regular treatment with some psychotropic or other drug apart from the trial medication, were all exclusion factors.

After being selected and giving consent, patients were withdrawn from their current neuroleptic medication and given placebo capsules for a minimum of two weeks for those on oral medication and four weeks for those on depot injectable preparations. Thereafter, patients were randomly assigned to treatment with chlorpromazine, propranolol or placebo for three months. Propranolol 40 mg, chlorpromazine 25 mg, and placebo were available in capsules of identical external appearance. The initial dose of medication was one capsule twice daily, increasing twice a week by one capsule twice daily, reaching a maximum dose of eight capsules twice daily (chlorpromazine 400 mg/day, propranolol 640 mg/day) within the first month. Occasional doses of diazepam were permitted but, with few exceptions, other drugs were avoided.

Pulse rate and sitting blood pressure were recorded twice weekly two hours after the morning dose of medication by nursing staff who were not involved in the clinical rating of the patients. A physician, also not involved in clinical rating, adjusted the dose of medication, when necessary, to prevent the pulse rate falling below 50/min or the systolic blood pressure falling below 90 mm Hg. A modified (Yorkston *et al*, 1974) version of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) was completed by a psychiatrist at baseline and monthly. The Nurse's Observation Scale for Inpatient Evaluation (NOSIE; Honigfeld *et al*, 1966) was completed by nursing staff at baseline, after two weeks and monthly. A 7-point global rating of severity of illness (normal; borderline, mildly, moderately, markedly, or severely ill; amongst the most extremely ill patients) and change of mental state (marked, moderate or slight improvement; no change; slight, moderate or marked worsening) was completed by the psychiatrist and nursing staff at baseline and monthly. The global rating of change at baseline was used to assess the change in mental state during the initial drug-free period. A 26-item side-effects inventory was completed at baseline and monthly.

Statistical Methods

The total score of the BPRS, the BPRS schizophrenia score (items conceptual disorganization, hallucinatory behaviour, unusual thought content, blunted affect, emotional withdrawal, suspiciousness, grandiosity, mannerisms or posturing, hostility and motor retardation from the BPRS), the total NOSIE score, the 'positive' NOSIE factors (social competence, social interest, personal neatness), and the 'negative' NOSIE factors (irritability, manifest psychosis, retardation) were subjected to analysis of covariance, with the baseline score for each parameter as the covariate and allowing for the effects of treatments, centres, and treatment by centre interaction. Further to the analysis of covariance, Dunnett's (1964) test was used to compare each of the two treatment groups in turn with the placebo group. In Dunnett's test a t-value between the placebo group and a treated group is calculated, the standard error of the difference being based on the residual mean square from the analysis of covariance. The significance level is calculated from Dunnett's tables rather than Student's t-test tables because Dunnett's tables allow for multiple significance tests being performed. Least square means and standard errors were calculated. These are means which have been adjusted to allow for the effect of the covariate and for the unequal numbers of patients in each group at each centre.

The scores on the 7-point scales were analysed using the non-parametric linear model of Bennett (1968) with a correction for ties, allowing for the effects of treatments, centres, and treatment by centre interaction.

Results

Twenty patients were from Parkside Hospital, 11 from St Edward's Hospital, 10 from Worcester Royal Infirmary and 12 from Holywell Hospital. There were no treatment by centre interactions at the 5 per cent

level of statistical significance, and therefore data were combined for statistical purposes.

Demographic and baseline data for patients included in the trial are shown in Table I. The three treatment groups are closely similar in age, sex distribution, and chronicity of illness. The baseline drug-free period was approximately 30 days, during which time the patients as a group showed little change in mental state, with some tending to worsen but others showing improvement. At the end of the initial drug-free period the three groups were closely similar in severity of illness as assessed by the BPRS and other scales. The most prominent symptoms in these patients were negative items on the BPRS (emotional withdrawal, blunted affect). However, significant positive symptoms were also present in that all but three patients were rated as showing at least mild to moderate degrees of hallucinatory behaviour, unusual thought content or conceptual disorganization. The overall severity of illness as rated by the psychiatrists at baseline was typically moderate or marked.

Three patients, all on propranolol, failed to reach the maximum dose of medication because of cardiovascular side-effects. These patients were maintained on their maximum tolerated dose of 240 mg/day in two cases and 480 mg/day in the third. Occasional doses of diazepam were given to six patients on chlorpromazine, five on placebo and three on propranolol. One patient took folic acid and temazepam, and one took chlorpheniramine, in addition to chlorpromazine; one patient was given Orovite (a multivitamin preparation) and one received a single dose of orphenadrine, in addition to propranolol. Otherwise, no additional medication was given.

Details of reasons for dropout are shown in Table II. Although there was a slight excess of dropout due to relapse in the placebo group relative to the propranolol or chlorpromazine groups, the differences did not reach statistical significance. The analysis of covariance of BPRS and NOSIE scores showed no significant differences between the three treatments at the 5 per cent level as assessed by the F-ratio for treatments. Similarly, the analysis of investigators' and nurses' assessment of severity or change in mental

TABLE I

Demographic and baseline data

		Chlorpromazine	Propranolol	Placebo
Sex	m	11	17	12
	f	5	2	6
Age (yrs, S.E.)		51.3 (2.3)	50.3 (2.9)	51.3 (3.1)
Age when first hospitalized (yrs, S.E.)		27.5 (2.8)	23.4 (1.3)	27.2 (2.2)
Time off drugs pre-trial (days, S.E.)		31.0 (4.3)	30.8 (2.7)	30.7 (3.7)
Change in mental state during baseline	improved	3	1	7
	no change	5	10	7
	worse	8	7	3
	not recorded	0	1	1
Pretrial BPRS total score (means, S.E.)		24.8 (2.4)	22.6 (2.0)	21.3 (2.1)
Pretrial doctor's global rating of severity of illness	borderline/mild	0	1	4
	moderate/marked	14	14	11
	severe/extreme	2	4	3

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TABLE II

Details of patients who left the trial prematurely

	Chlor-promazine			Pro-pranolol			Placebo		
	months			months			months		
	1	2	3	1	2	3	1	2	3
Relapse	3	1	0	0	3	1	2	4	1
Other*	1	1	0	0	1	1	2	0	0

* Side-effects, physical illness, need for extra drugs, withdrawal of consent.

illness showed no statistically significant overall treatment differences at the 5 per cent level. However, within these overall findings a number of trends were apparent.

Fig 1 shows the changes in BPRS schizophrenia scale and NOSIE total patient assets scale during the trial. Data on the NOSIE are given for only the first two months of the trial, as data from one centre were missing at three months so that least square means could not be calculated. On the BPRS schizophrenia scale, there is a non-significant trend for chlorpromazine to produce more improvement than placebo or propranolol by two months, although this trend is no longer apparent by the third month, possibly because the more seriously ill patients on propranolol or placebo had dropped out of the study by this time. No significant overall effects were seen on the NOSIE total patient assets scale, but propranolol was associated with significant deterioration ($P < 0.05$; Dunnett's test) in the sum of the 'positive' NOSIE factors (social competence, personal neatness, social interest) relative to placebo at one month.

Side-effects were considered to be drug-related only if an increase from baseline values had occurred. Due to missing baseline data and to a number of patients dropping out before the one month side-effects rating, this calculation could not be made in 17 cases. In the remaining cases, tremor occurred in 6/11 (55 per cent) of patients on chlorpromazine but only 1/13 (8 per cent) on propranolol and 2/12 (17 per cent) on placebo. Similarly drowsiness occurred in 6/11 (55 per cent) of patients on chlorpromazine but only 3/13 (23 per cent) on propranolol and 3/11 (28 per cent) on placebo. Otherwise there was no difference in distribution of side-effects between the groups. All side-effects were mild with the exception of one patient in the propranolol group who suffered a cardiovascular collapse requiring treatment with intravenous atropine.

The pulse and blood pressure measurements during

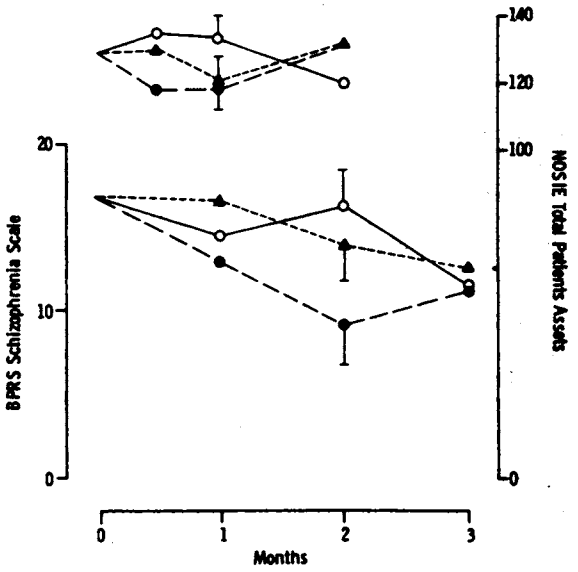

FIG 1.—Changes in scores on the BPRS schizophrenia scale and the NOSIE total patients assets scale (mean ± s.e.) during treatment with propranolol (▲ - - - -), chlorpromazine (● — —) or placebo (○ ——).

the trial period were averaged for each of the 51 patients in whom these data were available. The mean pulse rate in the propranolol treated patients (61.5 ± 2.1 SE) was significantly ($P < 0.01$; Dunnett's test) lower than in the placebo group (82.0 ± 1.6) with little overlap between the two groups. In contrast, the pulse rate in the chlorpromazine group (90.6 ± 3.3) was raised relative to placebo ($P < 0.05$) with 5 patients having a tachycardia greater than 100 beats/min. Systolic and diastolic blood pressure in the propranolol group (mean 116/71) and the chlorpromazine group (118/75) tended to be lower than in the placebo group (124/80), but there was a great deal of overlap between groups and only the difference in diastolic blood pressure between propranolol and placebo reached statistical significance ($P < 0.05$).

Discussion

We have demonstrated that propranolol has no important advantages over placebo in the treatment of chronic schizophrenic inpatients. This supports the previous finding of King *et al* (1980) in a smaller group of patients. The advantages of chlorpromazine over placebo were also minimal in this study. Thus, although there were individual exceptions, our patients as a group were chlorpromazine-resistant. This was confirmed in a subsequent study in which four of these patients were given propranolol in addi-

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tion to chlorpromazine which caused a marked increase in plasma levels of chlorpromazine but no corresponding clinical improvement (Peet *et al*, 1981). It is thus not likely that a higher dose of chlorpromazine would have been any more effective than the 400 mg/day used in this study.

The dose of propranolol used experimentally to treat schizophrenia has gradually fallen over the years. An average daily dose of 2990 mg/day was used by Atsmon *et al* (1972). Yorkston's group initially gave a median daily dose of 1125 mg/day (Yorkston *et al*, 1976) but mean daily doses of only 400–650 mg/day in subsequent controlled trials (Yorkston *et al*, 1977a, 1981). Efficacy has been claimed for doses of 320–640 mg daily (Ridges *et al*, 1977). We are therefore confident that we gave an adequate dose of propranolol. Of our patients 67 per cent had a mean pulse rate less than 64/minute: this level of pharmacological activity was considered necessary for anti-schizophrenic efficacy by Atsmon *et al* (1972).

Our patients were chronic schizophrenics with prominent negative schizophrenic symptoms such as emotional blunting, apathy, and social withdrawal. Positive symptoms were also present in most patients although these were often vestigial rather than florid. Crow (1980) has proposed an aetiological distinction between schizophrenics with predominantly negative symptoms (Type II) and those with predominantly florid positive symptoms (Type I). He suggested both on theoretical grounds and from clinical evidence that Type II patients are resistant to conventional neuroleptics. Our findings are consistent with this suggestion. This would indicate that large numbers of chronic schizophrenics with predominantly negative symptoms are being unnecessarily exposed to long-term neuroleptic treatment with the resulting risk of tardive dyskinesia.

It could be argued that neuroleptic-resistant patients are an unfair testing-ground for propranolol. However, earlier claims for the efficacy of propranolol specifically related to neuroleptic-resistant patients (Yorkston *et al*, 1974; Ridges *et al*, 1977; Hanssen *et al*, 1980). Two other factors which might be thought to have weighed against propranolol are the chronicity of illness and prominence of negative symptoms in these patients. Some workers have suggested that acute schizophrenics show more response to propranolol than chronic patients (Atsmon *et al*, 1972), but others reported good improvement in spite of prolonged chronicity (Yorkston *et al*, 1977a, b; Ridges, 1977; Hanssen *et al*, 1980). Yorkston *et al* (1976) and Sheppard (1979) suggested that negative schizophrenic symptoms are favourably influenced by propranolol. On the basis of these earlier studies, it would seem that we chose an appropriate group of patients for this trial. However, the results of these previous studies are at variance with our finding that propranolol has no effect on positive symptoms and may cause a deterioration in negative symptoms. There has been one controlled study of propranolol in the treatment of acute schizophrenic patients, in which Yorkston *et al* (1981) found that chlorpromazine had statistically significant advantages over propranolol. Thus, propranolol is apparently inferior to chlorpromazine in potentially neuroleptic-sensitive subjects.

The pattern of side-effects in our study is worthy of comment. Most notable were the cardiovascular effects: bradycardia with propranolol, and tachycardia with chlorpromazine. These effects were sufficient to compromise the double-blinding of the trial, making it necessary for cardiovascular monitoring and dosage adjustments to be conducted independently from the clinical assessment. This precaution was not taken in the early trial of Yorkston *et al* (1977a), leading to criticism (Tyrer, 1977). One patient taking propranolol in our study suffered cardiovascular collapse requiring urgent treatment with intravenous atropine. Normal clinical doses of propranolol have been used safely for many years. However, the increased risk of cardiovacular collapse with megadose propranolol suggests that such therapy is unacceptable for chronic schizophrenic patients with minimal nursing and medical supervision. The other prominent side-effects, drowsiness and tremor with chlorpromazine, are similar to those previously described as being the best discriminators between chlorpormazine and placebo (Guy *et al*, 1978).

In conclusion, there is no convincing evidence that propranolol is effective in the treatment of schizophrenia. The evidence from this trial suggests that propranolol as sole agent has no important advantage over placebo in chronic schizophrenic inpatients. Other work (Yorkston *et al*, 1981) indicates that propranolol is inferior to chlorpromazine in the treatment of acute schizophrenia. When propranolol is used as an adjunct to neuroleptics, any clinical improvement is likely to be due to a pharmacokinetic interaction leading to increased neuroleptic plasma levels rather than to any intrinsic anti-schizophrenic activity of propranolol (Peet *et al*, 1981). Even if propranolol were effective, its usefulness would be offset by the risk, with these high doses, of provoking cardiovascular disturbances.

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