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High-Dose Propranolol in Schizophrenia

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SUMMARY Eight male schizophrenics were treated in an open study with d.l. propranolol. The dose was increased by 160 mg/day until a maximum of 2,400 mg/day was achieved on day 15, and this remained constant until day 21. Seven patients showed significant clinical evidence of psychiatric improvement, while the incidence of toxic side-effects was low. There was wide inter-patient variation in plasma levels of propranolol. Despite a significant increase of plasma propranolol between day 15 and day 21 of the study, there was no significant change in serum prolactin.

A number of studies have presented evidence indicating that propranolol in high doses is effective in the treatment of schizophrenia (e.g., Atsmon *et al*, 1971; Yorkstone *et al*, 1976a; Yorkstone *et al*, 1977). These studies, however, have differed widely in both the type of drug regimens used and the severity of reported side-effects (Atsmon *et al*, 1971; Yorkstone *et al*, 1974; Yorkstone *et al*, 1976b; Yorkstone *et al*, 1977). In view of these variations, knowledge of plasma levels of propranolol might be expected to improve the management of high-dose propranolol therapy and therefore the relationship between plasma concentration of propranolol and clinical effect was investigated in the present study.

Propranolol, a β adrenergic blocker, has a chemical structure which is unlike that of existing neuroleptics, and if its proposed anti-schizophrenic property is confirmed it will be of some interest to compare its effect on brain biochemistry with that of existing drugs. One of the pharmacological actions of neuroleptics is blockade of central dopamine transmission, and this property, which may be responsible for the antischizophrenic activity (Matthysee, 1973), is also probably responsible for the observed increases in blood prolactin (Meltzer *et al*, 1976). The present literature dealing with the effect of propranolol on prolactin is inconsistent, however (Ridges *et al*, 1977; Hanssen *et al*, 1978; Nasrallah *et al*, 1977). In view of this, plasma prolactin concentrations were also measured in this study.

Method

Eight male patients, diagnosed as suffering from schizophrenia, were selected. Diagnosis was on the basis of: (a) Examination of case records and (b) The firm presence of at least 2 out of 10 Schneiderian first-rank symptoms, elicited at interview by the author (see Yorkstone *et al*, 1974). The ages of patients were between 26 and 46 years (see Table I). All had shown only a partial response to standard neuroleptic medication during their current episode of illness. Three of the patients were in an admission ward (cases 1, 2 and 3) and the remaining five were in the locked ward. In comparison with the locked ward patients, those in the admission ward were younger (mean age 28 years, compared with 39.6), had a shorter duration of current illness (1 year, compared with 16.5), and showed a shorter duration of illness since first onset (7 years compared with 19.6). Before entry into the trial, patients were screened for the presence of any physical illness which might have contraindicated treatment with propranolol. The patients' pre-trial medication, which (except for case 2) did not include depot neuroleptics, remained unchanged

throughout the study (see Table I). Cases 2, 4, 6, 7 and 8 were also receiving procyclidine.

The study lasted 21 days. On day 1, each of the eight patients received 40 mg, qds of propranolol. On each subsequent day, until day 16, the dosage was increased by 40 mg, qds. From day 15 until day 21, the dosage was kept constant at 600 mg, qds. Propranolol was administered daily at 8.00 a.m., 12 noon, 4.00 p.m., and 8.00 p.m. On days 6 (240 mg, qds), 10 (400 mg, qds), 15 (600 mg, qds) and 21 (600 mg, qds) blood was taken between 8.30 a.m.—9.30 a.m. to measure the plasma concentration of propranolol. Plasma propranolol was measured by a fluorimetric method (Shand *et al*, 1970). Additional blood was taken on day 15 (600 mg, qds) and day 21 (600 mg, qds), at the same standardized time (8.30—9.30 a.m.) to measure serum prolactin.

Written notes on each patient were recorded every day by: (a) the author on the basis of a semi-structured interview and (b) the nurse in charge of each ward, on the basis of observation and contact with the patients in the trial. At the end of the trial and after consulting the daily medical and nurse's notes, the author and nurse in charge of each ward jointly decided for every patient his optimum trial day, i.e., that on which he appeared to be the least psychiatrically ill. Blood pressure and pulse rate recordings were taken four times a day, half an hour before each dose of propranolol. If the blood pressure was less than 80/50 mms Hg or the pulse rate less than 50/minute, then both measurements were repeated half an hour later, at the time of medication. If either was still below the set limits, then that particular dose of propranolol was omitted; this omission was not corrected for in the next scheduled dose. Individual doses were also cancelled if any patient experienced discomforting or severe side-effects.

Patients were assessed on the day before the start of the trial and on its last day by the following scales:

(a) Brief psychiatric rating scale (BPRS), completed by the author. The BPRS (Overall *et al*, 1962) is an 18-item scale, each item being scored from 1 to 6. Five factors have been extracted from it: anxiety, depression, anergia, thought disturbance, activation and hostile sus-

TABLE I
Details of clinical features

Case No.	Age (years)	Number of 'first rank' symptoms		Duration of illness (years)	Duration of episode (years)	Present drug (daily dose)	
		pre-trial	post-trial				
1	31	3	1	10	1½	trifluoperazine	15 mg
2	26	3	0	6	½	fluphenazine decanoate	25 mg/3/52
3	27	3	0	5	1	pimozide	6 mg
4	46	4	4	24	20	trifluoperazine	15 mg
5	30	3	3	15	14	chlorpromazine trifluoperazine	150 mg 15 mg
6	41	5	5	19	18	haloperidol	60 mg
7	43	2	2	22	20	chlorpromazine haloperidol	1000 mg 40 mg
8	38	2	2	13	10	trifluoperazine	30 mg

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piciousness (Guy *et al*, 1975). For each patient, the total score and the score for each factor was determined, both pre-trial and at the end of the trial. The time span rated was the seven days before each assessment.

(b) Nurses' observation scale for in-patient evaluation; (NOSIE Honingfield *et al*, 1965); this is a 30-item scale, each item being scored from 5 to 9. For the majority of these items, the lowest score reflects the healthiest state and for these, the score was modified from 5 to 9 to 1 to 5. However, for the remaining items (4, 8, 9, 15, 17 and 20), the lowest score represents the most disturbed state and for these, the scoring was modified from 5 to 9 to 5 to 1. Seven factors have been extracted from the NOSIE, i.e. social competence, social interest, personal neatness, irritability, manifest psychosis, retardation and depression (Guy *et al*, 1976a). For each patient, the total score and the score for each factor was determined both pre-trial and at the end of the trial. The time span rated was three days before each assessment.

(c) A global scale (score 1 to 7) assessing psychiatric state (Guy, 1976b).

(d) A global scale to assess change in patients' psychiatric state (Guy, 1976b). The scoring on this seven-point scale (scale 1 to 7) was modified so that it extended from -3 through 0 to $+3$.

At the end of the trial (day 21), propranolol was continued in cases 1 to 7, but discontinued in patient 8 because of absence of any improvement. In each of those seven patients, dosage was then adjusted and individualized to correspond to that achieved on their respective optimum day. Six months after the trial's completion, the seven patients maintained on propranolol were reassessed on the basis of the following: (a) a semi-structured interview by the author and (b) medical and nurses' notes recorded during the six months interim.

Results

Using paired Student t tests, this group of eight patients showed statistically significant improvement in psychiatric state on all the four assessment scales:
BPRS $t = 3.93$, d.f. $= 7$, $p = <0.01$; NOSIE $t = 3.59$, d.f. $= 7$, $p = <0.01$; Global scale for psychiatric state $t = 5.07$, d.f. $= 7$, $p = <0.01$; Global scale for change in psychiatric state $t = 5.28$, d.f. $= 7$, $p = <0.01$. In addition, significant improvement occurred in two of the five BPRS factors ('anergia' $t = 4.32$, d.f. $= 7$, $p = <0.01$ and 'thought disturbance' $t = 3.12$, d.f. $= 7$, $p = <0.05$) and three of the seven NOSIE factors ('social interest' $t = 4.03$, d.f. $= 7$, $p = <0.01$; 'irritability' $t = 2.47$, d.f. $= 7$, $p = <0.05$; 'manifest psychosis' $t = 3.01$, d.f. $= 7$, $p = <0.02$). Two of the eighteen items on the BPRS, showed significant improvement; 'tension' $t = 2.67$, d.f. $= 7$, $p = <0.05$ and 'emotional withdrawal' $t = 2.67$, d.f. $= 7$, $p = <0.05$. However, only one of the thirty items on the NOSIE showed significant improvement; i.e. 'gets angry and easily annoyed' $t = 2.38$, d.f. $= 7$, $p = <0.05$. The change in psychiatric state scale showed that seven of the eight patients manifested overall improvement, while the remaining patient (no. 8), showed no significant changes. Of the seven patients who improved, four showed moderate improvement and three mild.

Four specific areas of improvement among these seven patients merit consideration in more detail:

(1) Tension and Aggression. All patients reported a feeling of calm during the trial, while the observations of both nursing staff and the author confirmed that they appeared calmer and more relaxed without being sedated. Also, there was a definite and sharp reduction in aggression in all the locked ward patients, who had been admitted there from open wards either because of unprovoked physical attacks on members of staff and/or because of gross and repeated destruction of property. In the locked ward, the combination of a substantial reduction in overt aggression and the development of a feeling of calm among the trial patients led to a significant overall improvement in the ward

atmosphere. This may well have been a major factor in the successful transfer and reallocation of patients to an open ward, when the locked ward was closed, shortly after this trial's completion.

(2) Mannerisms and Stereotypies. An appreciable decrease in the intensity and frequency of manneristic and stereotypic behaviour was seen during the trial in the only two patients (2 and 4) to exhibit these symptoms at the pre-trial assessment.

(3) Thought Processes. Four of the patients (1, 2, 3 and 7) reported an improvement in either their ability to 'concentrate' or their ability to 'think more clearly' and patient 1 reported that his mind was 'not wandering so much'. Also, the eight patients showed a statistically significant improvement in the BPRS 'thought disturbance' factor.

(4) Social and ward behaviour. For the majority, there was a discernable increase in constructive ward activity and this clinical observation was reflected in statistically improved changes in a number of the rating parameters—'anergia' (BPRS factor), 'social interest' (NOSIE factor) and 'emotional withdrawal' (BPRS item).

The pattern of overall improvement varied among the patients. For six (nos. 1, 2, 4, 5, 6, 7), there was progressive psychiatric improvement throughout the earlier part of the trial, reaching a peak on the optimum day. But thereafter, until the end of the trial, some progressive loss of achieved improvement.

The median optimum day was day 10 (range 9 to 21), the median oral dose on the optimum day was 400 mg, qds (range 360–600 mg) and the median plasma level of propranolol on the optimum day was 689 ng/ml (range 440 ng/ml to 1,536 ng/ml). No optimum day was more than one day from a recorded blood level.

TABLE II

Blood levels of Propranolol and Prolactin

Case No.	Blood levels of Propranolol and Prolactin (ng/ml)					
	Day No. 6 Oral dose of Propranolol 240 mg qds.	Day No. 10 Oral dose of Propranolol 400 mg qds.	Day No. 15 Oral dose of Propranolol 600 mg qds.		Day No. 21 Oral dose of Propranolol 600 mg qds.	
	Propranolol	Propranolol	Propranolol	Prolactin	Propranolol	Prolactin
1	354.5	691	828	27	928	28
2	354	692	787	21	—	14
3	391.5	1020	1098	38	1536	46
4	202	682	701	12	820	6
5	621	1095.8	1172	64	1385	53
6	409	550	677	62	708	62
7	243.5	625	689	40	730	44
8	281	682	720	46	917	30
Mean	357	752	834	38.75	1003	35.37

Key: — = not recorded.

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Toxic effects

Despite the high dosage of propranolol used, there was a low incidence of side-effects. Two of the patients (7 and 8) experienced no side-effects and of the remaining six, only three (3, 4 and 5) had sufficiently severe symptoms to warrant dose omissions. Patients 3, 4 and 5 had respectively seven, two and two doses of propranolol omitted; no dose omissions occurred in the 48 hours preceding blood collections.

The most frequent side-effects were drowsiness, ataxia and hypotension. In general, tolerance to the side-effects occurred quite rapidly, but the ataxia experienced by patient 5 (time of onset, day 18) became worse, even although the daily dose remained constant. Finally, patient 3 remarked that his side-effects seemed to be at their worst if he ate around the time of receiving a propranolol dose.

Excepting patient 3, who experienced side-effects early in the trial, all the observed toxic effects occurred after day 10. The minimum plasma level of propranolol associated with these latter, relatively late onset side-effects was 682 ng/ml. Of the three patients with the most severe side-effects, two (4 and 5) had the highest recorded plasma concentrations of propranolol.

Blood levels of propranolol and prolactin

There was a wide range of recorded plasma propranolol levels among the eight patients. Increasing oral dose of propranolol was associated with an increasing plasma level, but blood levels of propranolol also increased significantly between day 15 and day 21 ($t = 3.17$, d.f. $= 6$, $p = < 0.02$), despite the oral dose of propranolol being kept constant. No association was found between the plasma level of propranolol and scales of either overall psychiatric state or change in psychiatric state. Finally, despite the significant increase of propranolol between day 15 and day 21, there was no significant change in prolactin levels ($t = 1.25$, d.f. $= 7$, $p =$ NS).

Follow-up

At follow-up, six months after the trial's completion, the author's overall clinical assessment of the seven patients (1–7) maintained on propranolol was that their improvement had been maintained. In four of the seven (1, 2, 6, 7) there appeared to be evidence of further improvement, above that seen on day 21, to a level approximating that seen on their optimum day.

Discussion

The data presented in this paper indicate that, as a group, the eight patients showed statistically significant improvement in psychiatric state after treatment with propranolol. However, these results need to be interpreted in the light of the trial's obvious limitation, i.e., an uncontrolled non-blind design.

A main area of therapeutic change was the improvement in ward and social behaviour and the amelioration of anergia, lack of social interest and emotional withdrawal, which are symptoms integral to residual schizophrenia (Mayer-Gross *et al*, 1969). To date, orthodox neuroleptic treatment has been more successful in the treatment of acute schizophrenia than in the chronic residual states and if future studies confirm propranolol's beneficial effect on social behaviour and volition, this could represent an advance in existing pharmacological management. However, particular caution should be exercised in drawing conclusions from these improvements in social function because there is some evidence for believing that non-pharmacological (i.e. social and psychological) factors, which were not controlled in this study, have greater effects on social behaviour than on nuclear schizophrenic symptoms (Baker *et al*, 1977).

The absence of improvement in first-rank symptoms among the locked ward patients may have been related either to their long length of illness or to the fact that they were all diagnosed as suffering from paranoid schizophrenia. These speculations are in accord with other workers' observations (Yorkstone *et al*, 1976a).

Clinically, the most noticeable improvement seen was the patients' increased calmness and striking reduction in aggressive behaviour. In fact, in other studies in man, propranolol has been found to be beneficial in the control of somatic anxiety (e.g. Tyrer and Lader, 1974), psychic anxiety (Suzman, 1976), irritability

(Carlsson, 1976) and aggression (Elliott, 1977).

The following points concerning management of propranolol therapy arise from this study:

(a) The finding that each dose of propranolol was correlated with a wide range of blood levels, coupled with that of another study that there is a wide inter-patient variation in the ratio of plasma propranolol concentrations to brain propranolol concentrations in man (Myers *et al*, 1975), indicates that the therapeutic dosage may be similarly wide.

(b) The loss by six of the seven patients who responded to propranolol of some of their improvement, as dosage was increased beyond their optimum day, points to the possibility of a therapeutic ceiling, above which therapeutic benefit is lost. However, this may have resulted from the non-controlled factors operating in the study.

(c) The median optimum dose of 1600 mg/day was probably on the high side because dosage was increased every day until day 15, not allowing sufficient time for each interim dosage to maximize its blood level.

(d) Toxic side-effects were associated with high concentrations of plasma propranolol, especially when these levels exceeded approximately 700 ng/ml.

(e) The finding that all patients who improved showed a maximum benefit within 21 days of starting treatment is in contrast to the median response interval of eight weeks reported elsewhere (Yorkstone *et al*, 1976a).

(f) The enhancement of the bioavailability of propranolol by food (Melander, 1977) provides a plausible explanation for the association in patient 3 between severity of side-effects and food intake. Therefore, a constant relationship of propranolol treatment to food might improve the management of schizophrenia.

There are at least two criticisms of the finding that a significant increase of plasma propranolol was not associated with a significant change in serum prolactin. Firstly, co-existing neuroleptics may have directly interfered with the effect of propranolol on prolactin. Secondly, in the absence of a pre-trial serum prolactin measurement, it is impossible to know whether any effect of propranolol on prolactin had been realised before the first measurement of prolactin on day 15. However, if despite these criticisms further studies confirm this finding, it would suggest that propranolol may differ from other neuroleptics in not blocking central dopamine transmission. This conclusion would be in line with the majority of studies, including dopamine receptor binding studies, which have investigated the effect of propranolol on dopaminergic mechanisms (Laverty and Taylor, 1968; Green and Grahame-Smith, 1976; Burt *et al*, 1976). However, despite these findings, a few studies have claimed to have shown an effect of propranolol on dopamine (e.g. Wiesel, 1977).

Before a place for propranolol in the treatment of schizophrenia can be established, further controlled studies need to be carried out. If subsequent confirmation of propranolol's proposed action is obtained, additional studies might be conducted in order to determine its site of action, e.g., comparison of d.l. propranolol, which blocks noradrenergic transmission, with d. propranolol, which does not block noradrenergic transmission.

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