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Propranolol in Schizophrenia
II. Clinical and Biochemical Aspects of Combining Propranolol with Chlorpromazine

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Summary: Ten hospitalized chronic schizophrenic patients were given chlorpromazine alone and chlorpromazine plus high dose propranolol in two 7-week treatment periods according to a randomized crossover design. In the six patients who completed the whole study, plasma levels of chlorpromazine and chlorpromazine sulphoxide, total serum levels of neuroleptic and serum levels of prolactin were consistently and significantly elevated during treatment with chlorpromazine plus propranolol relative to levels during treatment with chlorpromazine alone. These effects are sufficient to explain previously reported clinical improvement in schizophrenic patients given propranolol in addition to neuroleptics.

In most of the published studies on the use of propranolol in the treatment of schizophrenia, propranolol has been given in addition to neuroleptics rather than as the sole agent. Used in this way, propranolol has been shown to be more effective than placebo (Yorkston *et al*, 1977; Lindström and Persson, 1980). However, the beneficial effects of propranolol in this situation could be due to an interaction with the neuroleptic rather than to a true antischizophrenic effect of propranolol. Such an interaction could be pharmacokinetic (increasing the available amount of active neuroleptic drug) or pharmacodynamic (enhancing the effect of the neuroleptic on the target receptors).

The possibility of a pharmacokinetic interaction is indicated by the finding of Vestal *et al* (1979) that subjects treated with propranolol show an increase in plasma propranolol levels when chlorpromazine is given in addition. Hanssen *et al* (1980) reported a decreased 4-hydroxypropranolol:propranolol ratio on adding thioridazine to existing propranolol treatment. This indicates that propranolol and phenothiazines may compete for hydroxylating enzymes. If so, it would be expected that the addition of propranolol to existing neuroleptic treatment would lead to an increased plasma level of neuroleptic. This might be expected to lead to an enhanced therapeutic effect of the neuroleptic, since there is evidence of a correlation between plasma levels and therapeutic effect of neuroleptic drugs (Sakalis *et al*, 1972; Curry, 1976; Rivera-Calimlim *et al*, 1976; Tune *et al*, 1980; Cohen *et al*, 1980).

The therapeutically relevant pharmacodynamic effect of neuroleptics—blockade of dopamine receptors—could be enhanced either by increased concentrations of the neuroleptic or by some direct potentiation of the neuroleptic by propranolol. Prolactin release is under central dopaminergic control, and increase of plasma prolactin levels has been used as an index of dopamine receptor blockade by neuroleptics (Langer *et al*, 1977). It has been reported that plasma prolactin levels may fall slightly during treatment with propranolol alone (Wilson *et al*, 1979; Hanssen *et al*, 1980), possibly due to blockade of central serotonin receptors by propranolol (Middlemiss *et al*, 1977). Treatment with a combination of propranolol and a neuroleptic results in elevated plasma prolactin levels (Hanssen *et al*, 1980) but it is not reported whether this differs from the prolactin response to a neuroleptic alone.

Based on these considerations, we predicted that blood levels of neuroleptic and prolactin would be higher during combined treatment with propranolol and chlorpromazine than during treatment with chlorpromazine alone. The present study was designed to test this hypothesis.

Methods

Subjects for the study were 10 (9 males and 1 female) informal in-patients aged 31–56 years (mean

45.4 years) with a diagnosis of chronic schizophrenia supported by application of criteria of Feighner *et al* (1972). The mean duration of hospitalization was 21.1 years (range 9–35 years). Patients with relevant physical illness, including heart disease, asthma, liver disease and diabetes were excluded, as were those patients with a history of alcoholism or drug dependence, or with a medical need for regular treatment with some psychotropic or other drug apart from the trial medication. Written informed consent was obtained from all the patients and from their nearest relatives when available.

All previous medication was stopped and the patients were immediately established on a fixed dose of chlorpromazine, which was individually determined on the basis of each patient's previous medication history. This dose was not altered during the 15 week study period. The study involved two 7-week treatment phases, separated by one week. During one 7-week period the patient was given chlorpromazine alone. During the other 7-week period, propranolol was added. The order of the two treatment phases was randomized.

The dose of propranolol was increased during the first four weeks to a maximum of 10 mg/kg/day unless the pulse rate fell below 50 per minute or the systolic blood pressure fell below 90 mm Hg, in which case the dose was not increased further or was reduced. The maximum attained dose of propranolol was then maintained for the next three weeks. Chlorpromazine was given three times daily (last dose 10.00 pm) and propranolol was given twice daily (last dose 5.00 pm). No other drugs were administered during the study. Pulse rate and blood pressure were recorded by nursing staff at least twice weekly, with the patient seated, two hours after the morning dose of medication. A modified (Yorkston *et al*, 1974) version of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) was completed by a psychiatrist and the Nurses Observation Scale for Inpatient Evaluation (NOSIE; Honigfeldt *et al*, 1966) was completed by nursing staff at the end of each 7-week treatment period.

Each week during the final three weeks of each treatment period, a blood sample was taken between 8.00 and 9.00 am, before the first morning dose of medication. Plasma levels of chlorpromazine, chlorpromazine sulphoxide and 7-hydroxychlorpromazine were measured by high pressure liquid chromatography (Stevenson and Reid, unpublished). The levels of neuroleptic in the serum (expressed as 'chlorpromazine equivalents') were also measured, using a minor modification of the radio receptor assay published by Creese and Snyder (1977), which measures neuroleptic levels in terms of their ability to displace (3H) spiroperidol from its receptor. Prolactin levels were measured by the method of McNeilly and Hagen (1974), and propranolol levels were measured using the method described by McAinsh *et al* (1978).

Because of the small number of subjects in the study and the difficulty in assuming normal distribution of the data, statistical analysis was performed using the sign test, to compare values during treatment with chlorpromazine alone with those during treatment with the combination of chlorpromazine and propranolol.

Results

Four patients failed to complete the study, one due to withdrawal of consent, one due to non-compliance with medication, one due to chlorpromazine side-effects and one due to cardiovascular effects of propranolol. Data prior to dropout were available for one of these four. For the patients completing the trial, the mean dose of chlorpromazine used was 6.7 mg/kg (range 2.5–13.8 mg/kg), and the mean maximum attained dose of propranolol was 8.1 mg/kg (range 4.6–10 mg/kg). In the six patients who completed the entire trial period, there were no consistent or significant changes in mental state as assessed by the BPRS, the NOSIE, and global ratings carried out by medical and nursing staff.

Details of plasma neuroleptic levels, which have been reported in part in a previous preliminary communication (Peet *et al*, 1980), and also plasma propranolol levels, are shown in Table I. It can be seen that, when propranolol is given in addition to chlorpromazine, there is a statistically significant increase in plasma levels of chlorpromazine parent compound, chlorpromazine sulphoxide and serum levels of 'chlorpromazine equivalent'. Increases in these levels were seen in every individual. Over the period of the three study weeks the mean plasma level of chlorpromazine tends to decrease when chlorpromazine is given alone, but to increase when propranolol is added, thus showing evidence of accumulation. Plasma levels of propranolol tended to increase over the three study weeks. Due to analytical difficulties, plasma levels of 7-hydroxychlorpromazine are best presented in qualitative rather than quantitative terms. During the three study weeks, 7-hydroxychlorpromazine was present in detectable quantities at some time in all patients given propranolol together with chlorpromazine but in only two out of the seven patients given chlorpromazine alone. However, all values were at or near the lower limit of detection and therefore these data are not reliable.

Details of serum levels of prolactin are shown in Fig 1. Prolactin levels showed a wide variation bet-

TABLE I

Plasma levels (ng/ml, mean and range) of chlorpromazine, chlorpromazine sulphoxide and propranolol, and serum levels of 'chlorpromazine equivalent', in patients given chlorpromazine alone or together with propranolol

	With propranolol			Without propranolol		
	Week 1 (n = 7)	Week 2 (n = 6)	Week 3 (n = 6)	Week 1 (n = 7)	Week 2 (n = 6)	Week 3 (n = 6)
Chlorpromazine	47.4 (10–166)	58.2 (8–115)	77.3* (41–135)	24.0 (0–36)	17.3 (0–26)	14.0 (0–30)
Chlorpromazine sulphoxide	20.7 (5–49)	20.7 (5–38)	22.8* (9–48)	6.7 (0–17)	3.3 (0–10)	1.7 (0–10)
Chlorpromazine equivalent	119.9 (67–162)	126.5 (51–201)	147.5* (121–191)	87.9 (0–178)	91.0 (22–131)	77.0 (0–118)
Propranolol	75.9 (42–109)	88.3 (13–136)	87.0 (27–171)	—	—	—

* With vs. without propranolol, P < 0.05 (sign test).

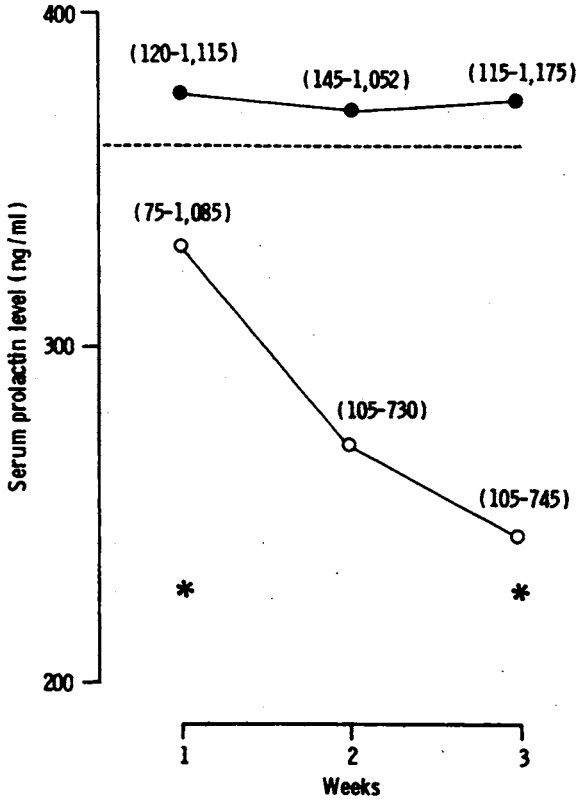

FIG 1.—Mean serum prolactin levels in patients treated with chlorpromazine alone (○) or together with propranolol (●). The range of scores is given in parenthesis at each point. Upper limit of normal shown as dotted line.
* With vs. without propranolol, P < 0.05 (sign test).

ween individuals but in every patient the level was elevated during treatment with chlorpromazine plus propranolol compared to the value during treatment with chlorpromazine alone (P <0.05 at weeks 1 and 3). On treatment with chlorpromazine alone, two of the seven patients had prolactin levels above the normal upper limit of 360 μg/ml but mean values for the group remained within the normal range; when propranolol was added, four of the seven patients had elevated levels and the mean prolactin level remained above the normal upper limit throughout the three study weeks. The addition of propranolol to chlorpromazine was associated in general with a fall in pulse rate and a slight fall in systolic and diastolic blood pressure. Other side-effects were not routinely recorded. Apart from one patient who developed marked extrapyramidal symptoms whilst taking chlorpromazine alone and a second patient who suffered a cardiovascular collapse whilst taking propranolol together with chlorpromazine, there were no clinically obvious side-effects.

Discussion

We have shown that plasma levels of chlorpromazine and its metabolites are markedly and significantly increased when propranolol is given in addition to chlorpromazine and that there is an associated increase in serum prolactin levels. Our hypothesis is thus confirmed.

As this study was primarily designed to investigate the biochemical parameters of treatment with propranolol and chlorpromazine, it was not considered necessary for treatment to be given on a double-blind

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basis. The clinical data must therefore be interpreted with some caution. However, a major beneficial effect of combining propranolol with chlorpromazine would not have been overlooked, and no such effect was apparent in this study.

A relationship between plasma levels of chlorpromazine and its therapeutic effect has been described by some workers (Sakalis *et al*, 1972; Sakalis *et al*, 1973; Curry, 1976; Rivera-Calimlim *et al*, 1976), whilst others have shown no such relationship (MacKay *et al*, 1974; Kolakowska, 1976; Wiles *et al*, 1976; Phillipson *et al*, 1977). A therapeutic range for chlorpromazine plasma levels has been suggested, with either too high a level or too low a level leading to lack of clinical response. Curry (1976) suggested that this range lay between 30 and 400 ng/ml, whereas Rivera-Calimlim *et al* (1976) suggested a range from 50 to 300 ng/ml. Of the patients who completed our study, only two subjects achieved plasma levels greater than 30 ng/ml when given chlorpromazine alone, whereas all six subjects achieved this plasma level when given propranolol in combination with chlorpromazine. Propranolol thus had the effect of elevating plasma levels from below the putative therapeutic range to within this range.

It is likely that effectively the same increase in plasma levels of neuroleptic could be produced more simply by increasing the dose of chlorpromazine. High dose chlorpromazine has been shown to be more effective than conventional doses in a small proportion of hospitalized chronic schizophrenic patients (Prien and Cole, 1968; Clark *et al*, 1972). However, in these studies the benefits of high-dose chlorpromazine were seen only in patients under the age of 40 years who had been hospitalized for less than ten years. As only one of our patients fell into this cateogry it is perhaps not surprising that the increase in plasma chlorpromazine levels produced by propranolol did not lead to clinical improvement.

Chlorpromazine has over 30 identified metabolites and many of these are active pharmacologically (Usdin, 1971). Two principal metabolites are 7-hydroxychlorpromazine which is biologically active and chlorpromazine sulphoxide, which is biologically inactive (Creese *et al*, 1978). A number of workers have found that responders to chlorpromazine have relatively greater amounts of 7-hydroxychlorpromazine than chlorpromazine sulphoxide in their plasma (Sakalis *et al*, 1973; MacKay *et al*, 1974; Phillipson *et al*, 1977). In our study, both the active and the inactive metabolite showed an increase on adding propranolol to the chlorpromazine, although the plasma levels of 7-hydroxychlorpromazine could not be adequately quantified due to technical difficulties. Because chlorpromazine has several active metabolites, it is not surprising that reported correlations between therapeutic response and plasma levels of parent drug, with or without its main active metabolite, are not strong. It would be expected that the combined effect of other active metabolites would also be important in determining clinical response. The radio receptor assay used in the present study is therefore of great interest, since this assay measures all active drug, whether parent compound or metabolites. It has been reported that there is a lower threshold for neuroleptic efficacy in that patients with serum levels of neuroleptic under 50 ng/ml show a poor clinical response (Tune *et al*, 1980). All of our patients had serum levels of chlorpromazine equivalent greater than 50 ng/ml, even before the introduction of propranolol, and in all cases the introduction of propranolol led to a marked increase in serum level of chlorpromazine equivalent.

The level at which this pharmacokinetic interaction between propranolol and chlorpromazine occurs is uncertain. It has been previously shown that coadministration of chlorpromazine with propranolol leads to a marked increase in plasma levels of propranolol (Vestal *et al*, 1979), and this interaction may be due to competition for hydroxylating enzymes (Hanssen *et al*, 1980). In the present study, plasma levels of 7-hydroxychlorpromazine were very low with or without the presence of propranolol. The marked increase in plasma levels of chlorpromazine sulphoxide in the presence of propranolol may indicate that chlorpromazine metabolism was diverted down this metabolic pathway. Our findings are thus compatible with a relative inhibition by propranolol of hydroxylation of chlorpromazine, although other metabolic steps may also be involved. Our findings with chlorpromazine cannot automatically be generalized to other neuroleptics but these drugs share many metabolic pathways (Cooper, 1978) and therefore similar interactions between propranolol and other neuroleptics can be predicted.

There have been a number of studies on plasma prolactin levels during treatment with neuroleptics. It has been shown that plasma prolactin levels are markedly increased on acute administration of neuroleptics (Nikitopoulou *et al*, 1976; Wiles *et al*, 1976; Langer *et al*, 1977; Meltzer *et al*, 1977; Gruen *et al*, 1978). Whilst a number of workers have found elevated prolactin levels even after chronic administration of neuroleptics (Beumont *et al*, 1974; Wilson *et al*, 1975; De Rivera *et al*, 1976; Kolakowska *et al*, 1976; Gruen *et al*, 1978), these effects were less clear-cut than those following acute administration of neuroleptics, and there is evidence that a degree of tolerance develops to the prolactin-releasing effect of neuroleptics (Kolakowska *et al*, 1976; Naber *et al*,

1980). In the present study, prolactin levels during treatment with chlorpromazine alone were mainly within normal limits, although two subjects showed elevated levels. All these patients had been treated with dopamine-receptor blocking drugs for a number of years and therefore had probably developed some tolerance. However, all patients were capable of enhanced prolactin response, as shown by the consistent increase in plasma prolactin levels when propranolol was added to the chlorpromazine. Propranolol alone has little effect on prolactin levels in man, if anything producing a slight decrease (Wilson *et al*, 1979; Hanssen *et al*, 1980). The increase in plasma prolactin levels which we observed when propranolol was added to chlorpromazine was therefore almost certainly caused by the increase in plasma levels of chlorpromazine and its active metabolites.

We have demonstrated that there is a pharmacokinetic interaction between chlorpromazine and propranolol, such that plasma levels of chlorpromazine and its active metabolites increase markedly when propranolol is given in addition to chlorpromazine. This in turn enhances the pharmacodynamic effect of chlorpromazine on dopamine receptors, as evidenced by increased prolactin release. It is therefore likely that the enhancement of therapeutic effect which can occur when propranolol is added to a neuroleptic (Yorkston *et al*, 1977; Lindström and Persson, 1980) is due to increased plasma levels of neuroleptic rather than to a true anti-schizophrenic effect of propranolol.

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