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"Continuous" Thioproperazine

A Controlled Trial in Chronic Schizophrenia

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Thioproperazine ('Majeptil') is a recently introduced phenothiazine derivative which readily produces extra-pyramidal disturbances. Its pharmacology was originally described by Courvoisier *et al.* (1958) and its clinical properties by a number of workers including, in this country, Denham and Carrick (1961). Several investigators have reported impressive results with this drug in a variety of mentally ill patients, including chronic schizophrenics who had failed to respond to other forms of therapy.

Opinions differ on the importance of the extra-pyramidal disturbances, and the drug has been administered in different ways, according to the view of the particular investigator. Maurel *et al.* (1960) in France and Denber *et al.* (1959) in America, considering the extra-pyramidal disturbances to be merely troublesome side-effects, have used the drug in an orthodox "continuous" manner, suppressing the side-effects either by reducing the dosage or by introducing an anti-Parkinsonism drug. Delay *et al.* (1959) and Denham and Carrick, on the other hand, have advocated the deliberate production of extra-pyramidal disturbances, having observed a high correlation between the appearance of such phenomena and therapeutic response. In order to minimize distress to the patient and difficulties in management, Delay *et al.* introduced the "discontinuous" method of administration, giving the drug in short courses of four to five days with rest periods between. This latter method and the impressive results reported have led to speculation concerning the possible mechanisms involved. In a *Lancet* annotation (1961), for example, the results obtained by Denham and Carrick are discussed, and tentative suggestions made of a possible association between the schizophrenic process and disturbances in the brain stem.

This drug, therefore, seems to be of some interest, not only because of its therapeutic possibilities, but also because of the speculation as to its mode of action. So far, however, claims for its efficacy have been based on uncontrolled studies. That such uncontrolled studies are unreliable, particularly in the case of psychotropic drugs, has been amply demonstrated by the studies of Foulds (1958) and Fox (1961). Nevertheless, most workers have apparently felt that, because of the easily observable side-effects of this drug, adequately controlled investigations were not feasible.

It seemed to us, however, that if the appearance of obvious extra-pyramidal disturbances could be adequately precluded by simultaneous exhibition of an anti-Parkinsonism agent, it should be possible to conduct a properly controlled trial of thioproperazine used in the "continuous" manner.

In this paper we report on such a trial.

The anti-Parkinsonism drug chosen was benzhexol hydrochloride ('Artane') and it was necessary first to determine whether this preparation itself had significant psychotropic actions. As a side-issue of the main study we were able to make some assessment of the usefulness of benzhexol as a suppressor of drug-induced extra-pyramidal disturbances.

Material and Methods

Choice of Patients

130 male chronic schizophrenics were reviewed. All those who were physically fit and in whose case it was agreed there was no doubt

about the diagnosis were selected. Medication was stopped for at least one month. One investigator now examined these patients in detail, noting age, duration of illness, previous treatment, present clinical state and average score on a behavioural rating scale. With these data, the other investigator matched patients in pairs, allocating one of each pair to Group A, which was to receive the active drug, and the other to Group B, which would receive the dummy tablets. Two groups of 18 were thus selected. So far as previous treatment was concerned, all at some time had received at least 12 weeks of chlorpromazine in doses of not less than 100 mg. t.i.d. and some had either longer periods or larger doses or both. Almost all had received one or more courses of E.C.T., half had had deep insulin therapy and eight had prefrontal leucotomies. All had made only partial response to various treatments.

Method

The intention was to carry out the trial using a "double blind" technique, neither the patients nor those carrying out the assessments knowing who were receiving the active drugs. Four patients did, however, show transient extra-pyramidal disturbances at some time during the trial and it is recognized that because of this the investigation was not completely blind as far as nurses' ratings were concerned. Throughout, the investigator who had matched the patients held the "key" in order to be in a position to manipulate the dosage and to deal with any side-effects, but took no part in assessing the results. He aimed at suppressing the appearance of extra-pyramidal disturbances as fully as possible. All patients remained in their usual environment during the investigation and care was taken to ensure that no change was made in their daily routine. Patients not on active drugs received equivalent doses of identical dummy tablets.

The investigation was carried out in four stages:

Stage I No treatment was given for 1 month.

Stage II Group A received benzhexol in a dose of 10 mg. per day for 3 weeks, while Group B received dummy tablets.

Stage III Group A now received thioproperazine in addition to the benzhexol. The dose was increased in the first 2 weeks to 80 mg. per day and maintained where possible at this level for a further 4 weeks. In 4 patients who showed extra-pyramidal signs on this regime the dose of thioproperazine was reduced slightly and that of benzhexol slightly raised. Group B patients received equivalent doses of dummy tablets.

Stage IV All treatment was discontinued for 2 weeks.

Clinical assessment was carried out and behavioural rating scales completed during the last week of each stage.

Six weeks after the completion of the trial Group A patients were given thioproperazine alone. The number who now developed extra-pyramidal disturbances on doses not exceeding 80 mg. per day was compared with the number who had shown such effects in Stage III when benzhexol was being given in addition. Some idea of the efficacy of benzhexol as a suppressor of drug-induced extra-pyramidal disturbances was thus gained.

Assessment

Assessment was made both by behavioural rating scales completed by the nursing staff and clinical assessment by the "blind" investigator. The Baker and Thorpe Behavioural Rating Scale (1956) was chosen because it was considered to be objective and easily scored by the nursing staff. Several weeks of trial runs were held to acquaint everyone concerned with the use of the scale. During this preliminary period it was found that the tenth item on the scale, which is concerned with assessing "friendliness", was difficult to score and there was considerable inconsistency in marking. The scale was therefore modified by omitting this item and thus consisted of 9 different items of behaviour. Each item was scored from 0, indicating normality, to 4, indicating the most deteriorated behaviour.

Rating was carried out daily for 5 full days in each week under study and the weekly scores noted.

The clinical assessments were based on a roughly standardized interview and scored as much improved; slightly improved; unchanged; worse.

Results

Thirty-four of the original 36 patients completed the trial. One from Group A was withdrawn when X-ray revealed pulmonary tuberculosis, and one from Group B took his own discharge.

(A) *Rating Scale Scores*

Group scores for the full scale and for each item of behaviour were calculated. Statistical analysis by Student's "t" test showed no significant differences between the scores obtained by the active and control groups at any stage of the trial, nor were differences in scores within either group at the various stages found to reach significant levels.

Although the individual scores obtained in this study appeared to be normally distributed, doubt has been cast on whether they should be regarded as such and whether, therefore, it is appropriate to apply Student's "t" test. A further analysis of the results was therefore carried out by applying a χ^2 method to the numbers of patients improved or not improved at each stage. Again no significant differences were found.

Because of the lack of positive results only the total scores for the final week of each stage are shown here.

	Stage I	Stage II	Stage III	Stage IV
Group A	628	518	671	581
Group B	696	583	627	609

(B) *Clinical Assessments*

The condition of each patient at the end of Stage I, when all treatment had been discontinued for one month, was taken as the standard against which he was assessed as the trial progressed. The results are shown in the Table.

There is obviously no real difference between treatment and control groups at the end of Stage II. Neither benzhexol nor dummy tablets produced any significant change which could be detected clinically. At the end of Stage III, however, 11 of the patients receiving thioproperazine and benzhexol were judged to have shown slight improvement compared with no improvement in the control group. Applying χ^2 to the numbers improved or not improved, this difference is found to be highly statistically significant [$\chi^2=13\cdot44$ ($p < 0\cdot001$)].

These findings are discussed below.

(C) *Suppression of Extra-pyramidal Disturbances*

During Stage III of the trial, 4 of the 17 Group A patients receiving thioproperazine and benzhexol showed transient extra-pyramidal disturbances. Fifteen of this group were later given thioproperazine alone in similar dosage. Of these, 9, including the above 4, now showed extra-pyramidal effects. The remaining 6 showed no disturbance even when the dose was increased beyond 80 mg. per day.

	Stage II		Stage III	
	Group A (Benzhexol)	Group B (Dummies)	Group A (Thioproperazine + Benzhexol)	Group B (Dummies)
Much Improved	0	0	0	0
Improved	1	0	11	0
Unchanged	14	12	2	13
Worse	2	5	4	4

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Side-effects

No noticeable side-effects developed in patients receiving benzhexol alone. Of those on both active drugs one developed superficial venous thrombosis and another a carbuncle. These conditions responded rapidly to treatment and it was not necessary to withdraw the patients from the trial. Seven patients from this group showed anorexia with marked weight loss and several others appeared pale and unwell, although general physical examination and haemoglobin estimation revealed no specific abnormality. Four patients on the active preparations showed extra-pyramidal disturbances despite the use of benzhexol.

Discussion

Although the behavioural rating scale failed to show any change, clinical assessment indicated that a significant number of patients had improved on the active preparation. We would emphasize, however, that the improvements were slight. This contrasts with the results reported from previous uncontrolled studies, for example Maurel *et al.* claimed that of 98 schizophrenics treated in the "continuous" manner, 53 were greatly improved and 19 improved. Moreover, like Ollendorff (1962) and Crammond (1962), we encountered a high incidence of disturbing side-effects although all patients rapidly recovered after the drug was withdrawn. From this study, therefore, our conclusion must be that thioproperazine used in the "continuous" manner is not a particularly suitable or effective treatment in chronic schizophrenics.

Nevertheless, a number of patients, previously resistant to therapy, did appear more alert and sociable and communication became easier. Some ceased to show stereotyped behaviour and mannerisms which had been present for years. These changes suggest that the drug merits further investigation. It may be that it is more effective used in the "discontinuous" manner and our preliminary studies in this direction would seem to suggest this.

Finally, although it is not possible to draw statistically valid conclusions from the small numbers involved, our investigation of benzhexol would suggest that it is an effective suppressor of drug-induced extra-pyramidal disturbances.

Summary

In a controlled trial of thioproperazine ('Majeptil') used in the "continuous" manner, involving two matched groups of chronic schizophrenics, we have been unable to repeat the impressive results of other uncontrolled studies. Although, used in this way, the drug produced certain interesting changes in a number of patients, the overall improvement obtained was insufficient to justify its long term use in view of the disturbing side-effects.

Benzhexol ('Artane') appeared to be an effective preparation with which to suppress the extra-pyramidal effects induced by thioproperazine, and was found to have negligible psychotropic action.

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