THIOTHIXINE (NAVANE): AN UNCONTROLLED CLINICAL TRIAL ON 28 CASES OF SCHIZOPHRENIA

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INTRODUCTION

Thiothixine is a derivative of thioxanthine. There are two basic structural differences between thioxanthines and phenothiazines: (i) the nitrogen (N) atom in the tricyclic nucleus is replaced by carbon (C) and (ii) the side chain is attached to the nucleus by a double bond that prohibits any rotation of the first carbon in the chain.

Animal studies have shown that thiothixine is a potent anti-emetic and that it interferes with conditioned avoidance learning in low doses. It exhibits only weak anticholinergic, antihistaminic, hypotensive, hypothermic and sedative properties. The results suggest that thiothixine may be useful in chronic psychotic excitation with active delusions and hallucinations (1).

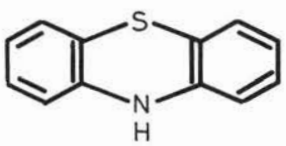
Numerous uncontrolled clinical trials (2–10) with acute and chronic schizophrenics indicate that thiothixine is an effective antipsychotic agent. The symptoms most frequently reported to have improved were suspiciousness, thought disorder (conceptual disorganisation), hallucinations, tension, unusual thought content, emotional withdrawal and excitement (agitation). Subjects were also noted to have shown improvement in social competence and personal neatness.

Controlled studies (11–14) however, have not indicated that thiothixine is superior to the more commonly known phenothiazine compounds such as trifluoperazine, chlorpromazine, perphenazine and thioridazine.

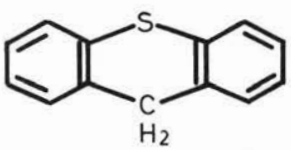
The aim of our study was mainly exploratory. We hoped to evaluate the short-term efficacy and toleration of thiothixine in the treatment of hospitalised schizophrenic patients.

Selection and Characteristics of Patients

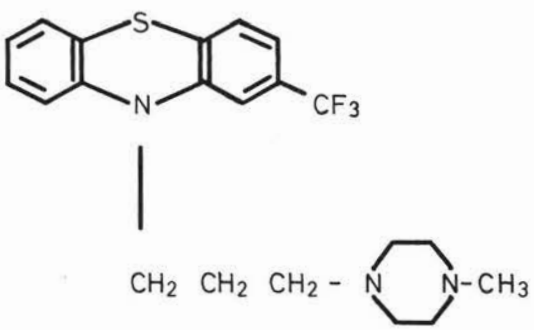
Consecutive female admissions to Tampoi Mental Hospital with a diagnosis of schizophrenia, during the period of 18th September to 19th October, 1969, were considered for inclusion in the trial. The criteria used in diagnosis were the presence of at least two of the following symptoms:– thought disorder, auditory hallucinations, flattening or incongruity of affect, and feelings of passivity. Patients below the age of 12 and those with epilepsy, galucoma, anaemia, liver



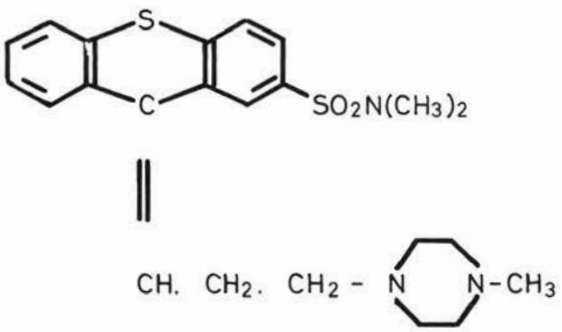
PHENOTHIAZINE



THIOXANTHINE



TRIFLUOPERAZINE



THIOTHIXINE

failure, leucopaenia and sensitivity to thiothixine were exlcuded.

Initially thirty patients were admitted to the trial, but two were subsequently excluded because they received electro-convulsive therapy. Of the remaining 28, there were 11 first admissions and 17 readmissions. (mean readmission figure: 2.4). Their mean age was 32 with a range of 14–47 years. 24 were engaged in domestic duties housewife or helping at home), and 19 (68%) were married.

METHOD

Previous specific medication, if any, was discontinued at least one week prior to starting on thiothixine. Assessment of the patients' symptoms, using a modified Gorham Brief Psychiatric Rating Scale, was done at the following intervals:–

a) immediately before commencing treatment with thiothixine and
b) after 7, 14, 30 and 60 days treatment with thiothixine.

At each of the above intervals, independent ratings of the patients' symptoms were made by all four assessors. The mean score (to the nearest whole number) for each symptom was computed and recorded.

During the trial, no other psychotropic drugs, with the exception of symptomatic remedies for the control of side effects (benzhexol), acute excitation (paraldehyde), and insomnia (sodium amytal) were administered.

Depending upon the severity of symptoms on admission, subjects were started on 10–20 mg/day orally of thiothixine. The dosage was increased if necessary, judging on the response, until the optimum dose for each patient was determined. The recommended maximal dose of 60 mg. daily was not exceeded. Except for those on 10 mg. daily, medication was administered in two divided doses per day. Table I shows the mean dose per patient at each assessment (rating) interval.

Before treatment and at the end of the trial, the following laboratory investigations were carried out on each patient:– full urine examination, haemoglobin, total white and differential blood count, blood urea and liver function tests.

RESULTS

(i) *Gorham Brief Psychiatric Rating Scale*

The sum of mean ratings on target symptoms at each assessment interval is shown in table II.

Table I

Time Interval(Days)	0	7	14	30	60
Mean Daily Dose/Patient (mg.)	13.6	25.4	35.0	33.9	27.1
Range (mg.)	10–20	10–40	20–60	20–60	10–60

Table II

Symptoms	Time (Days) 0	7	14	30	60	No. of Patients rated as having symptom	
						Pretrial	Post Trial
Somatic Concern	11	11	11	6 (p. 02)	5	10	4
Anxiety	5	6	5	0	1	4	1
Emotional Withdrawal	47	30	21(p. 001)	16(p. 001)	10	25	8
Conceptual Disorganisation	37	10(p. 01)	3(p. 001)	3	4	23	3
Guilt Feelings	0	0	0	0	0	0	0
Tension	40	11(p. 001)	4(p. 001)	4	4	24	4
Mannerisms & Posturing	20	4(p. 001)	0	0	0	12	0
Grandiosity	6	3	0	0	3	3	2
Depressive Mood	9	11	8	0(p. 001)	1	8	1

Hostility	27	4	4(p. 001)	6	0	17	0
Suspiciousness	32	7(p. 001)	5	3	3	19	3
Hallucinatory Behaviour	59	21(p. 001)	10(p. 001)	6	4	24	2
Motor Retardation	23	27	20	7(p. 001)	6	16	5
Uncooperativeness	25	7(p. 001)	4	1	0	16	0
Unusual Thought Content	20	3(p. 001)	0	0	0	13	0
Blunted Affect	52	44	42	33(p. 01)	26	26	28

The results were analysed using the uncorrelated test for all the data. The ratings at 0 day were taken to be the controlled group and subsequent ratings at 7th, 14th, 30th and 60th day were assumed to be independent.

At the end of 7 days treatment, a significant improvement ($P < 0.001$) was noted in the ratings of tension, suspiciousness, hallucinatory behaviour, uncooperativeness, unusual thought content and mannerisms and posturing. This improvement was maintained in each category throughout the trial. Symptoms of emotional withdrawal, conceptual disorganisation and hostility showed a significant and sustained improvement after 14 days treatment; and in the case of depressive mood and motor retardation, only after 3 days. The symptoms which did not appear to have been influenced in this trial were somatic concern, anxiety (subjective), grandiosity and blunted affect.

(ii) *Overall Therapeutic Effect*

At the end of the trial, the overall therapeutic effect was assessed for each patient on a five point scale: marked improvement, moderate improvement, slight improvement, no change, worse. The results are shown in Table III

Table III

Degree of Improvement	No. of Patients	%(N = 28)
Marked	10	36
Moderate	9	32
Slight	6	21
No change	3	11
Worse	0	0

A total of 19 cases (68%) were rated as having shown marked or moderate improvement at the end of the trial. Slight improvement was noted in 6 patients, and 3 remained unchanged. None was rated as having become worse.

(iii) *Side Effects*

Side effects were reported in 20 patients (71%). They were of moderate severity in 11 cases and mild in 9. The frequency of their occurrence is shown in Table IV.

Table IV

Side Effect	No. of cases reported
A. Extrapyramidal	
Rigidity	15
Tremor	5
Akathesia	2
Gait	2
Dystoxia	2
Oral Dyskinesia	1
B. Autonomic	
Salivation	1
Constipation	1
C. Central	
Sedation	1
Insomnia	1
Hyperactivity	1
Lactation	1

The most frequently occurring side effects were of the extrapyramidal type, with rigidity and tremor predominating. In all except two cases, they were controlled by the administration of benzhexol.

Autonomic and Central side effects were infrequent and did not unduly interfere with the treatment regime. Stilboestrol was effective in controlling the case with lactation.

(iv) *Laboratory Findings*

One patient, aged 20, with a history of two previous admissions, was found to have leucopaenia (total white count 3,5000; polymorphs 30%, cosinophils 4%, lymphocytes 64%, monocytes 2%) at the end of the treatment period. Her blood picture was normal on admission. She had no past history of allergy and during her previous admissions, she was treated with chlorpromazine without adverse effect. Chlorpromazine was reintro-

duced, and blood investigations including platelet count obtained a month later were within normal limits.

No abnormal laboratory investigations were found in the other 27 patients.

DISCUSSION

The results reported in this study have to be interpreted in the context of an uncontrolled clinical trial. The recording of the mean score (of all four assessors) for each target symptom may minimise errors in clinical observation and evaluation, but does not eliminate rater bias. Though the trial patients were not segregated in a special ward, the nursing staff were aware that they were receiving a new drug. In addition to the greater degree of attention and observation, the patients were subjected to more investigations than the routine admissions.

Nevertheless, the main findings appear to reflect the observations reported in earlier uncontrolled trials (2–10), which reported significant improvement in "schizophrenic" symptoms: hallucinatory behaviour, suspiciousness, thought disorder, mannerisms and posturing, negativism (uncooperativeness), tension and emotional withdrawal (indifference to environment). Unlike the report of Kurland et. al (6), blunted affect was not observed to improve in the present study. This could be explained by the erroneous interpretation of facial rigidity (a side effect) as blunting of affect

Depressive mood and motor retardation improved significantly after 30 days. This finding supports the contention of Goldstein (15) and overall (16), that thiothixine may be useful in the treatment of patients with depression. In this area, thiothixine has the added advantage of the ability to control tension and to activate anergic patients.

As reported in previous studies (2–16), extrapyramidal symptoms were the most frequently observed side effects. Their appearance was not correlated with clinical improvement. They were of mild to moderate severity and did not significantly interfere with treatment, autonomic side effects were rare. Restlessness (hyperactivity) and insomnia, reported in 80% of patients in one study (8) was seen only, in two cases (7%). Lactation, a side effect unreported in previous studies and occasionally encountered with the use of phenothiazines, was noted in one patient.

The discovery of leucopenia in one patient on thiothixine is worth noting. Laboratory studies carried out on a total of 412 patients in previous studies (2–16), have not revealed this abnormality, though photosensitivity has been reported in one patient by Goldstein (8). It is interesting that the leucopenia improved, despite the substitution of chlorpromazine.

In conclusion, the present sutdy on 28 patients appears to confirm that thiothixine is an effective antipsychotic agent, useful in the management of schizophrenia especially those cases not responding to phenothiazine. Its range of activity may be compared to that to trifluoperazine, with which it has a close structural resemblance. The antidepressive properties suggested in the results of this and other studies deserve further inquiry. Like the phenothiazines, unwanted reactions e.g. blood disorders may occur.

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GROUP PSYCHOTHERAPY IN COMBINATION WITH PSYCHOTROPIC MEDICATION

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INTRODUCTION

Group psychotherapy has been generally accepted as a method of treatment in psychiatry and is at present a well established field of psychotherapeutic procedure undertaken in many psychiatric centres all over the world. However as this treatment was derived from Western thought and ideas, Asian therapists who utilize group psychotherapy should carefully adapt the procedure to the cultural background of the patients.

Since psychotropic medications have been introduced in the field of psychiatry, the progress in therapy has clearly revealed that a number of patients have recovered and gone back to their community faster than ever before. Unfortunately, the rate of relapse has also been high. Thus Hoch (1958) suggested that the combination of group psychotherapy and psychotropic medication would prevent relapsing of the patient. Many papers have been published with regard to the benefit of group psychotherapy in combination with psychotropic medications; Bindelglas and Goline (1957) found that chlorpromazine and reserpine facilitated relatedness, awareness in the course of group psychotherapy with psychotic female patients. Winkleman (1959) also found trifluoperazine effective as an aid to short-term group therapy. Borowski and Tolwinski (1969) found combined treatment with chlorpromazine and group therapy more effective than chlorpromazine alone and particularly "in the quality of the improvement obtained and the speed of disappearance of such symptoms as delusional thinking and lack of insight."

Therapeutic Setting

This report deals with the experience of group psychotherapy in two countries; Malaysia and Thailand. In Thailand, group psychotherapy was introduced in Srithunya Hospital, Nondhaburi in 1963 (Suwanlert 1964), as a method of treatment for psychiatric patients, and also in Hospital Permai, Tampoi, Malaysia in 1972. Malaysia and Thailand are different both traditionally and