EXPERIENCE WITH THIORIDAZINE ("MELLERIL") THERAPY

By

N. GOLD, M.B., B.S., D.P.M.

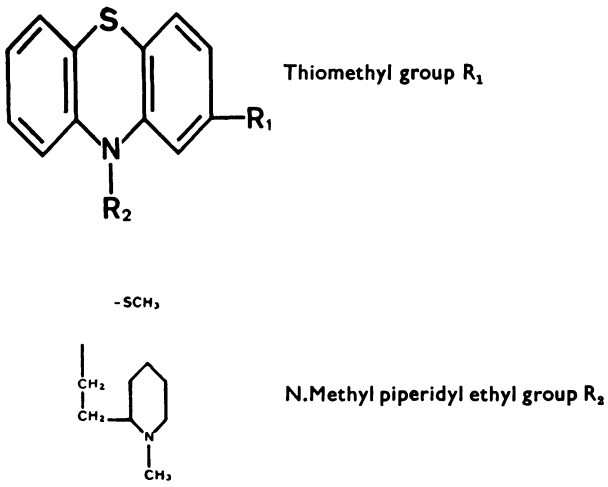
Senior Registrar

Park Prewett Hospital, Basingstoke

"A doctor must know not only the virtue of a drug, but also its drawbacks"—
Carling (1960).

THIORIDAZINE is one of the newer phenothiazine derivatives used in psychiatry. Previous workers have reported few serious side-effects with it. The following pilot trial was carried out on male patients suffering from chronic schizophrenia who required nursing in a closed ward.

PHARMACOLOGY



Phenothiazine basic structure

Thioridazine possesses the basic phenothiazine structure with a thiomethyl group at position 2 and a N.Methyl piperidyl ethyl group at position 10 (see figure). It is claimed that substitution of a N.Methyl piperidyl ethyl group at the 10 position abolishes most of the adrenolytic and anticholinergic activity of the drug.

Thioridazine has little anti-emetic effect, is less effective in producing hypothermia and is not so powerful a sedative, comparing these effects with

https://doi.org/10.1192/bjp.107.448.523 Published online by Cambridge University Press

other phenothiazines, particularly chlorpromazine. Taeschler and Cerletti (1959) having done considerable work on the pharmacology of thioridazine suggest that the absence of extra-pyramidal side-effects is related to the difficulty in producing catalepsy in experimental animals.

Selection of Patients

Thioridazine has been used both in psychotic and neurotic disorders and has been recommended for hyperkinetic, violent, agitated, anxious and assaultive patients. Smith *et al.* (1959) used thioridazine with success on patients who were refractory to previous therapy. In view of this it was decided to carry out a trial on schizophrenic patients who were in the only locked male ward.

As thioridazine was only available in tablet form, patients who were likely to be reasonably co-operative (and take the tablets) were selected and because of this only 23 were suitable.

Age distribution	21–30	31–40	41–50	51–60
	2	9	8	4

Their duration of hospitalization ranged from 2 to 22 years.

Medication at the time of trial included promazine, perphenazine, chlorpromazine, trifluopromazine, promethazine, paraldehyde, barbiturates and lithium citrate. All the patients were regarded as having failed to have benefited from these treatments. Six patients had been leucotomized during the period 1949–54. Electroplexy had been given in the past.

Ward structure does not include a protective room.

The entertainment provided includes a weekly cinema show and a weekly dance in the main hall; in the ward TV, radio, billiards, snooker and table skittles are available and weekly "closed ward" socials which entail visits to or from the corresponding female ward.

The patients perform domestic work in the ward, O.T. work is carried out in the ward and O.T. centre. Some patients work on the hospital farm.

All these factors were constant during the trial.

Drug Dosage

Following Sandison (1960) it was begun at 50 mg. t.d.s. It was increased gradually until most of the patients were on 400 mg. a day. Three were further increased to 600 mg. a day in divided doses after four weeks.

Assessment of the Patients

Behaviour Rating

A rating scale, modified from Baker and Thorpe (1956) was used to measure deterioration and restlessness to see if the drug therapy improved the patients.

Rating was done by the multiple observer method using the charge nurses and staff nurses who knew the patients very well. They were continually on the alert for any alteration in the patient. The 23 patients were divided into one group of 11 and another of 12 so that the smaller groups enabled the direct

https://doi.org/10.1192/bjp.107.448.523 Published online by Cambridge University Press

observation method to be more accurate. Each charge nurse and staff nurse on both shifts observed different groups from 7 a.m. until 10 p.m., thus obtaining four independent ratings for each patient over a two-day observation period. (Stencilled scales were filled in independently and each observer put his results into an envelope which was sealed and handed in at the end of the shift.) The night staff recorded detailed observations on the patients from 10 p.m. to 7 a.m.

RATING SCALE

	4	3	2	1	0
A	Motionless.	Occasional movement.	Very retarded.	Slightly retarded.	Normal.
B	Wildly excited —needs isolation all day.	Needed isolation for a short period.	Restless all day.	Restless for a short period.	
C	Tube fed.	Spoon fed.	Eats only with persuasion.	Finicky with food.	
D	Mute.	Occasional word with persuasion.	Speaks only if spoken to.	Occasional spontaneous remark.	
E	Needs dressing fully.	Needs help in dressing.	Dresses self but needs adjustment.	Dresses self but untidy.	
F	Does no work.	Works with supervision in ward.	Works with supervision outside ward.	Works without supervision	
G	Doubly incontinent several times.	Doubly incontinent once.	Incontinent of urine several times.	Incontinent of urine once.	
H	Aggressive several times without provocation.	Aggressive once without provocation.	Aggressive several times when approached.	Aggressive once when approached.	
I	Has no friends.	Friendly towards one of staff.	Friendly towards one patient.	Friendly towards two people.	
J	No interest in entertainment.	Rarely interested in entertainment.	Occasional interest in entertainment.	Frequent interest in entertainment.	
K	Always hallucinated and/or deluded.	Frequently hallucinated.	Sometimes hallucinated.	?Hallucinations.	

A 5-point Rating Scale with 0 Equal to a Normal Response and 4 the Most Abnormal Response

Daily assessments on each patient were performed for a week while they were on their previous medication.

After this all drugs were stopped and the daily assessments continued for a period of three days. Thioridazine was then commenced and assessments were continued twice weekly for thirteen weeks. While on maximum dosage the thioridazine was suddenly stopped and the ratings were continued for a further four weeks.

https://doi.org/10.1192/bjp.107.448.523 Published online by Cambridge University Press

Standardized Interviews

These were also carried out at the beginning of the trial and eight weeks later by the investigator. Each patient was interviewed separately in the ward clinic and a number of questions which were unlikely to produce an emotional reaction in the patient were asked and the responses noted.

Laboratory Investigations

Using the method of Leach and Crimmin (1956) regular examination of the urine was done to determine if the patients were absorbing thioridazine. Total white blood counts and differential counts were performed at six weeks and twelve weeks.

Results

One aggressive patient who had required regular paraldehyde medication, mean daily dose 4·5 drachms (range 4–8), was controlled while on thioridazine on a lower dose, mean 1 drachm, for some days no paraldehyde was given. No windows were broken during the trial nor were there any attempts to escape by the 23 patients. Night reports were generally of peaceful nights, the exceptions were due to patients not on thioridazine therapy.

Hollister and McDonald (1959) found weight changes in their patients while on thioridazine and during the trial these were noted as follows: 16 patients gained weight by 2 to 18 pounds, mean 8 pounds, most of these were in the younger age group. Six patients lost weight, 2 to 8 pounds, mean 3 pounds, most of these were in the older age groups. The weight of one patient was unchanged. Of the patients who had undergone leucotomy, three gained and three lost weight.

Repeated blood counts showed mostly normal total white cells, 7 had a relative lymphocytosis. Three had a slight leucocytosis, up to 13,000 c.mm. on one occasion. Leucopenia was not found. Urine analysis proved that thioridazine was being absorbed by all patients.

Ophthalmoscopy did not reveal retinal changes, the dosage was considerably below that used by May *et al.* (1960) who have reported retinal pigmentation and oedema.

It had been thought that toxicity to the retina could be prevented by the use of a sulphur-containing radical replacing a halogen at position 2 on the phenothiazine nucleus.

No extrapyramidal involvement or jaundice was seen. Photosensitivity did not occur in spite of frequent and prolonged exposure to strong sunlight while on 400 and 600 mg. a day, this contrasts with the report by Kent (1960).

There were no subjective complaints of a dry mouth or nasal stuffiness. When staff supervised the tablets being swallowed they noticed that the mouths were generally moist.

The standard interview did not reveal any significant change in the patients.

The rating scores gave a high measure of agreement by the observers.

Assessing the results of Behaviour Rating showed 6 patients unchanged, 2 more were retarded without any benefit and 15 made an improvement on their initial ratings by one point. Of these 15, 6 became more retarded but showed other improvement. Seven patients improved in more than one characteristic (see Table).

https://doi.org/10.1192/bjp.107.448.523 Published online by Cambridge University Press

TABLE

Results of Changes in Behaviour Rating

Patient 1	..	..	A	0–1	Patient 10	..	..	A	0–1
								B	2–1
								C	1–0
2	..	..	A	0–1				E	1–0
								F	4–3
								H	1–0
3	..	..	F	4–3				I	2–1
								J	3–2
4	..	..	A	1–2	11	..	..	A	0–1
			D	2–1				B	1–0
								F	3–2
								J	2–1
5	..	..	D	3–2					
			F	3–2	12	..	..	A	1–2
								F	3–2
								H	1–0
6	..	..	D	2–1				J	3–2
7	..	..	D	3–2	13	..	..	A	0–1
			J	3–2				B	1–0
8	..	..	A	0–1	14	..	..	I	2–1
			F	3–2					
			J	2–1					
					15	..	..	F	3–2
9	..	..	E	2–1	16	..	..	I	2–1
			F	3–2					
					17	..	..	F	3–2

A	B	C	D	E	F	H	I	J
8	3	1	3	2	9	2	3	5

While the improvement in working ability agreed with the findings of Haug (1959) the retardation noted is contrary to his findings.

WITHDRAWAL EFFECTS

During the four-week period after the drug was stopped, 11 patients who had improved became disturbed and were recommenced on thioridazine. One patient who had not shown any improvement while on the drug was worse without it and was improved when treatment recommenced. Five who had improved maintained their improvement for four weeks after cessation of drugs.

One patient during the first three days had 2 withdrawal fits, having previously been on barbiturate therapy.

Asymptomatic hypotension was detected in one patient—his records revealed that he had been hypotensive two years before; no cause was found for this.

DISCUSSION

No blind trial was used because of the numerous objections to the placebo response (it has been commented that the investigator is the only one who

https://doi.org/10.1192/bjp.107.448.523 Published online by Cambridge University Press

does not know when the active or inert substance is being used in a drug trial).

Instead all the patients who were accustomed to the ward and had been on numerous therapies prior to this trial received thioridazine, which was just another white tablet to them. In this way they were used as their own controls and were assessed before, during and after the cessation of thioridazine therapy.

Multiple observers were used to minimize observer bias. Although it is not possible to prevent contamination due to the observers hoping for improvement, they were frequently reminded that only the side-effects were being sought. The drug was not boosted as a panacea.

The continued improvement of the five patients off treatment might be due to altered habits during the course of the trial.

A recent review by Hurst (1960) of phenothiazine derivatives which are in current use in psychiatry does not deal with thioridazine. It gives as the three most serious side-effects parkinsonism, jaundice and agranulocytosis.

The parkinsonian syndrome may be associated with chlorpromazine, perphenazine, fluopromazine, trifluoperazine and prochlorperazine. Jaundice may occur with chlorpromazine, pecazine and acepromazine. Chlorpromazine, promazine, pecazine, trimeprazine and methotrimeprazine may cause agranulocytosis.

From the present trial the absence of any serious side-effect agrees with the findings of Sandison *et al.* (1960). It appears that thioridazine used in doses similar to chlorpromazine is a safe and effective phenothiazine derivative.

Summary

Twenty-three male chronic schizophrenics in a closed ward were treated with thioridazine for 13 weeks. No side-effects were noticed except for slight drowsiness. Two patients were worse and 6 were unchanged; 15 improved.

Alterations in weight occurred but were not related to the clinical picture.

Thioridazine produced drowsiness as its only side-effect in daily doses of 400 to 600 mg.

When the drug was stopped, 11 became worse and were put back on thioridazine.

Acknowledgments

My thanks are due to Dr. I. Atkin and Dr. E. C. Turton for permission to carry out this trial and the nursing staff of M.6 for their willing co-operation. Sandoz Products Ltd. generously supplied thioridazine tablets.

References

Baker, A. A., and Thorpe, J. C., *J. Ment. Sci.*, 1956, **112**, 840.
Carling, E. R., *The Medico-Legal Journal*. Vol. XXVIII, Part II, p. 65.
Haug, J. O., *Tidsskrift for den Norske Laegeforening*, 1959. **79**, (6), 317.
Hollister, L. E., and McDonald, B. F., Communication at California Medical Association. February, 1959.
Kent, D. A., *Brit. Med. J.*, 1960, 5189. 1–1888.
Leach, H., and Crimmin, W. R. C., *J. Clin. Path.*, 1956, **9**, 164.
May, R. H., Selymes, P., Weekley, R. D., and Potts, A. M., *J. Nerv. Ment. Dis.*, 1960, **130**, 230.
Sandison, R. A., Personal communication, 1960.
Idem, Whitelaw, E., and Currie, J. D. C., *J. Ment. Sci.*, 1960, **106**, 732.
Smith, J. A., Christian, D., Rutherford, A., and Henderson, H. C., Scientific Exhibit. American Psychiatric Association. P.A. April 27.
Taeschler, M., and Cerletti, A., *Nature*, 1959, **811**, 823.
Hurst, L., *J. Ment. Sci.*, 1960, **106**, 443, 755.

https://doi.org/10.1192/bjp.107.448.523 Published online by Cambridge University Press