CLINICAL TRIALS WITH MELLERIL (TP21) IN THE TREATMENT OF SCHIZOPHRENIA

A Two-Year Study

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The Background of the Study

The authors undertook to investigate the effects of two new phenothiazine derivatives on schizophrenic patients. Over a period of two years a series of clinical trials have been carried out on approximately 260 patients, some controlled, some uncontrolled. These drugs, known as Melleril (TP21) and KS75 are chemically related. Although Melleril was ultimately selected as the drug of choice we have, for statistical reasons, included some of the findings with KS75.

Chemistry and Pharmacology

Table I shows the relationship of Melleril to other phenothiazines.

Melleril therefore differs from the known phenothiazine derivatives by the substitution of a thiomethyl group in position 2 of the phenothiazine ring. In addition, an N-methyl-piperidyl-ethyl side chain is attached to the cyclic nitrogen at position 10. It is known that substitutions in positions 2 and 10 are of particular significance for the pharmacological and clinical action of these compounds.

In spite of the extensive side-chain modification the drug still possesses properties basically similar to chlorpromazine, and is effective in similar doses. It seems, however, to be the side chains which are concerned with some of the side-effects of the phenothiazines. For example, if R_1 is H and R_2 is $-CH_2CH(CH_3).N(C_2H_5)_2$ we have an anti-parkinsonian agent, Ethopropazine (lydivane). Alteration of the ring structure as in Tofranil, N(γ-dimethylaminopropyl)-iminodibenzyl hydrochloride or imipramine, on the other hand, radically alters the clinical properties of the compound, and produces an anti-depressant drug.

According to Taeschler and Cerletti (1958) using mice and rats as their experimental animals it was found that Melleril reduced spontaneous motor activity in the mouse. This inhibitory effect was much more marked if the mouse had been pre-treated with amphetamine and was therefore hyperkinetic. This

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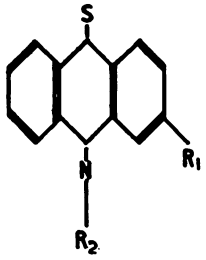
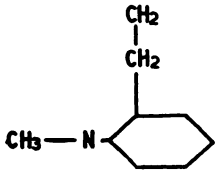
TABLE I



Basic phenothiazine structure

where R_1 is:-	and R_2 is:-	Substance
– Cl	$-CH_2.CH_2.CH_2.N(CH_3)_2$	Chlorpromazine
$-O-CH(CH_3)_2$		KS75
$-S-CH_3$	As KS75	Melleril

effect was greater than the inhibitory effect of Melleril on physiological hyperactivity. On the other hand, Melleril reduced hunger drive in mice significantly only when the mice were irregularly fed and were fasting moderately. In rats the conditioned flight response was not influenced by small doses (2 mg./kg.) of Melleril if the stimulus motivating this reaction persisted and reinforced the response. Without the reinforcement the inhibitory effect of the drug was in evidence with small doses.

These observations tend to show that Melleril does not elicit a general sedative effect. Amphetamine-induced excitation, hunger drive occurring outside the routine feeding time and an unnecessary flight response are more readily depressed than the more immediate response to hunger, shock and environmental adaptation. It would also be important to note that Melleril is able to inhibit an emotional reaction in the rat (emotional defecation) in doses which are well below the ones which are necessary to prevent a conditioned escape reaction, whereas the contrary is true for chlorpromazine and even more so for perphenazine.

Taeschler and Cerletti further compare their pharmacological findings with chlorpromazine and conclude that whereas the effects of Melleril and chlorpromazine on the autonomic nervous system are similar, Melleril is much less effective as a sedative and hypothermic agent and that about 10 times the dose of Melleril is required to produce the same degree of catatonia in the rat.

Less is known about the pharmacology of KS75. The limited information available to us suggests that the autonomic responses in animals are similar to Melleril.

The Design of the Clinical Trials

Reliable clinical evaluation of any new drug is notoriously difficult in psychiatric practice. Drugs which affect mental processes, such as mood and thinking, are liable to produce widely differing results in differing environments. It has sometimes been suggested that drugs such as the phenothiazines whose actions are dependent on environment cannot really be effective. These critics are referring to the difficulties experienced in measuring the clinical results.

Numerous investigations (e.g. Foulds, 1958) have drawn attention to the fact that uncontrolled trials unduly favour the apparent clinical response to the psychotropic drug being investigated. On the other hand, the inability of controlled trials to demonstrate the superiority of pharmacologically active drugs over their placebos is well known. We therefore consider that a favourable clinical impression does not by itself prove that a drug is useful any more than a statistically negative controlled trial proves that the drug is of no use. If, however, two or more investigators working as independently as possible in the same hospital, obtain a positive result with a drug both by long-term clinical use and by controlled trial, this is as far as one is ever likely to be able to go in establishing "proof" of the efficiency of the drug. This is what we have done in this trial, and we would emphasize the importance of clinical impressions with a new drug provided the investigators have already carried out several drug trials and are experienced with the use of drugs having similar pharmacological properties to the drug under trial.

We carried out four controlled trials in the wards of this mental hospital in which we endeavoured to stabilize the environment of the patients as carefully as possible. In addition to the environment, the other problem which affects psychiatric clinical trials is the method of rating or assessing mental changes during drug treatments. We designed a scale (to be reported elsewhere) which depends solely on information obtained by the doctor at the time of interview with the patient. This information can be scored as a numerical total, the higher the score the greater being the deviation from normal. This total can be broken down under eight headings—Memory, Awareness and Orientation, Perception, Sleep, Thought, Affect, Reality and Behaviour. It is a four-point scale with 53 items, some of which are mutually exclusive, the scoring range extending from 0–129. In practice scores of over 100 are very exceptional and 80 indicates a severe degree of psychiatric abnormality. Two of us (E.W. and R.A.S.) who rated the patients throughout the trial correlated well when both rated 10 schizophrenic patients ($r=0\cdot89$; when $P=0\cdot01$, $r=0\cdot76$).

The controlled trials were double blind and statistically controlled. They were carried out in various wards of the hospital, each trial being confined to one ward. Neither the nursing staff nor the authors, who rated the patients, knew whether the patients were on the drug or its placebo. The placebo tablets were of the same size, shape, colour and taste as the active tablets. Each trial lasted for twelve weeks, and the dispenser who kept the code, randomized the patients. The patients were all schizophrenics and were either chronic or subacute relapsing types. The only exception was the inclusion of two old G.P.I.s, one in each group in the trial with chronic patients. During the first week each patient was given 150 mg. of Melleril or its placebo daily in three divided doses. After the first week the dose was built up to 300 mg. daily in three divided doses and standardized at 300 mg. daily for the rest of the trial. This method, by establishing tolerance, avoided excessive drowsiness and lethargy and 300 mg.

daily appears to be the most satisfactory long-term dose in this type of patient. Patients who have recovered and are receiving long-term maintenance treatment as out-patients require less Melleril, 150 mg. daily being the optimum dose.

These controlled trials established that Melleril in the doses given resulted in a statistically significant improvement occurring in schizophrenic patient compared with the placebo. We also concluded that Melleril was therapeutically somewhat more efficacious and produced fewer side-effects than KS75. We therefore continued our clinical trials with Melleril and at this point abandoned KS75.

These subsequent trials which were uncontrolled consisted of long-term trials with Melleril in relapsing schizophrenics, lasting up to 2 years. They were designed chiefly to examine the long-term results of treatment, particularly having regard to toxicity, side-effects and dosage. This class of schizophrenic patient was selected as in all cases the response of previous attacks to other forms of treatment was known. Thus to some extent the patient was his own control.

Results of the Trials

First Phase

Four double-blind trials in chronic and sub-acute schizophrenics. The results are summarized in Table II.

A further analysis of the eight different items on the rating scale showed that in trial number 3 with Melleril and placebo the scores for thought disorder were significantly improved, whilst there was no significance concerning the other fields of mental activity. This suggests that Melleril causes an important improvement in thought disorder, but does not disprove change in other types of mental activity as in some cases the possible range of scores was too small to make a t-test sufficiently sensitive.

It will be noted that the matching of the patients in the two groups which are compared is adequate. All the patients were considered to be schizophrenic and the mean scores in the two groups were very nearly equal before the trial began. All the ratings were done by two of us (E.W. and R.A.S.) but patients in any one trial series were only rated by one investigator.

Second Phase

Twenty-four patients were selected for long-term study. They were all schizophrenics and had all originally been in hospital where they had commenced treatment with Melleril. Furthermore in every case these patients had previously been treated with E.C.T., deep insulin, chlorpromazine or, in one case, leucotomy either singly or severally. Some had had reserpine and other major tranquillizers. These treatments had either failed to produce improvement or else relapse had occurred after initial improvement. All 24 patients were able to leave hospital and have succeeded in remaining out for at least 6 months whilst continuing to take Melleril. They were all invited to attend the hospital for a global assessment by two of us (J.D.C. and R.A.S.). The Powick Rating Scale was not used, as the scores would have been too low. We assessed the patients in terms of "Not improved", "Improved" and "Much improved". Generally speaking the assessment "Much improved" was only made if the patient was in full-time employment and had no appreciable symptoms. The duration of treatment with TP21 varied from

TABLE II

Results of the Four Double-Blind Trials with Melleril and KS75

Trial	Type of Patient	Drug	No. of Patients	Mean Age	Mean Duration of Illness in Years	Mean Score Before Trial on P.R.S.*	Mean Score at End of Trial	Mean Difference	Value of t Statistic	Significance
1. 26 weeks trial of KS75 and placebo	Over-active chronic deteriorated schizophrenics. Males	KS75 ..	15	52	23	53	44	−8·8	1·2	None
		Placebo ..	15	47	19	53	52	−2·9		
2. 12 weeks trial of KS75 and placebo	Relapsing schizophrenics	KS75 ..	9	35	5	36	26	−9·8	2·0	Barely significant (P=0·06)
		Placebo ..	7	40	5	33	34	+1·6		
3. 12 weeks trial of Melleril and placebo	Relapsing schizophrenics	Melleril ..	8	33	6	36	26	−10·5	2·6	Significant (P=0·02)
		Placebo ..	7	37	5	38	45	+4·6		
4. 12 weeks trial of Melleril and KS75	Chronic but not deteriorated schizophrenics	Melleril ..	16	38	6	30	20	−9·9	Zero	None
		KS75 ..	15	44	6	27	17	−9·9		

* Powick Rating Scale

6 months to 2 years, the average being about 10 months. Twenty out of the 24 patients, 18 men and 2 women, attended and each was assessed by the 2 investigators on the same day (4 patients declined to attend). The results are tabulated in Table III. It will be noted that this is a group of patients selected for their failure to respond to treatment and that the results are very gratifying. These patients tolerated Melleril in doses of 150 mg. daily very well indeed with a commendable absence of side-effects, drowsiness being the one of which patients most frequently complained.

Discussion of the Results

Ninety-two patients took part in the controlled trials of whom 24 received Melleril. As mentioned above, 24 further patients took part in the long-term trial all of whom received Melleril. About another 150 patients received Melleril in doses varying from 100 to 500 mg. daily, but for various reasons it has not been found possible to group them in a way that can easily be presented. Much was learnt, however, from these 150 patients and the authors concluded that Melleril was superior to all other phenothiazines in its ability to bring about clinical improvement in florid and overactive schizophrenics with the minimum of side-effects.

These results may be compared with the findings of other clinicians who have reported on Melleril. Cohen (1958) treated 29 psychotic patients who required management of their hyperactivity, delusional thinking or anxiety with improvement in 62 per cent. and a commendable absence of side-effects. The dose varied from 100 to 400 mg. daily given over 3–92 days. Hollister and Macdonald (1959) reported their results in 104 psychiatric patients with a variety of illnesses, chiefly schizophrenic reactions. Of 14 patients treated in a double-blind study with successive 1-month courses of drug or placebo, 9 patients improved on the drug and only 1 on placebo. In the remainder 100–400 mg. daily produced results comparable with other potent phenothiazine tranquillizers, but only minimal side reactions were observed, chiefly drowsiness, dizziness and nasal stuffiness. In doses of 2,000 mg. extra-pyramidal effects, seizures and excitement did not occur. Fleeson *et al.* (1958) conducted a placebo trial with 60 out-patients using Melleril and KS75. Twenty-three of these patients suffered from psychoneuroses, 30 from psychosis and the remainder were classed as "sociopathic reactions". Twelve out of 15 patients treated with Melleril were improved, a result significantly better than that obtained with KS75 or with the placebo. Kinross-Wright (1958) reported on the use of Melleril in 198 institutionalized and ambulatory patients in a wide range of disorders ranging from severe psychotic disturbances to minor nervous and functional disorders. The drug was well tolerated in doses of 75 mg. to 2,400 mg. daily. Side-effects were notably absent, and it was noted that some patients forced to interrupt treatment with other phenothiazines because of extra-pyramidal symptoms were able to continue therapy with Melleril without the appearance of parkinsonism. The results were best in the acute psychotics, but chronic psychotics and neurotics also derived considerable benefit.

Effects of Melleril in Psychosis

Our work to date suggests that acute and subacute schizophrenia, particularly of the paranoid and floridly symptomatic type, responds best to Melleril. In many cases, however, long-standing cases have improved and in all cases of schizophrenia except those which are completely apathetic and burnt out

TABLE III

Follow-up of Long Term Patients Who were Discharged on TP21

Case No.	Sex	Age	Diagnosis	Response to TP21 Assessed by		Duration of Treatment with TP21	
				R.A.S.	J.D.C.		
1	F	27	Hebephrenia	Improved	Improved	2 years	
2	M	24	Schizophrenia	Much improved	Improved		7 months
3	M	38	Schizophrenia	Much improved	Much improved	1 year	
4	M	28	Schizophrenia	Much improved	Much improved		11 months
5	M	27	Schizophrenia	Improved	Improved		7 months
6	M	29	Schizophrenia	Much improved	Much improved	1 year	10 months
7	M	36	Paranoid schizophrenia	Improved	Improved		10 months
8	M	37	Paranoid schizophrenia	Much improved	Much improved		10 months
9	M	27	Schizophrenia	Much improved	Much improved		10 months
10	M	33	Schizophrenia	Much improved	Much improved		6 months
11	F	28	Relapsing schizophrenia	No change	No change		11 months
12	M	32	Schizophrenia	Improved	Improved		10 months
13	M	26	Schizophrenia	Much improved	Much improved	1 year	2 months
14	M	16	Schizophrenia	Much improved	Much improved		7 months
15	M	36	Paranoid schizophrenia	Improved	Improved	1 year	3 months
16	M	32	Paranoid schizophrenia	Much improved	Much improved	1 year	4 months
17	M	32	Paranoid schizophrenia	Much improved	Much improved		11 months
18	M	22	Schizophrenia	Improved	Much improved		9 months
19	M	27	Paranoid schizophrenia	Much improved	Much improved		6 months
20	M	38	Schizophrenia	Improved	Improved		7 months

some improvement can be expected. This is particularly true in the case of paranoid schizophrenia and paraphrenia, and a number of long-standing cases are now living at home and leading a useful social life free of symptoms whilst continuing to take Melleril. Depression does not respond and may be made worse. The manic phase of manic depressive psychosis can be controlled but the subsequent depressive phase is not prevented despite continued treatment. Puerperal psychosis responds provided depressive features are absent. Melleril has a place in the geriatric field and of 9 elderly confused and overactive patients who received Melleril, 6 received benefit. In the chronic wards of the hospital Melleril is highly successful in controlling anti-social and aggressive behaviour without any great incidence of side-effects.

Side-Effects of Melleril

The side-effects which we have observed during trials with Melleril have not been of a serious nature and we believe that the claim can justly be made that Melleril has fewer side-effects than any other of the phenothiazine compounds.

Generally speaking the side-effects of the phenothiazines can be grouped under 5 headings:

1. Those associated with the anti-cholinergic effects of the drug.
2. Parkinsonism and extra-pyramidal symptoms.
3. Allergic responses and water retention phenomena.
4. Disturbances of liver function.
5. Disturbances of autonomic function probably the result of pituitary depression.

These are the common ones. Others such as granulocytopenia and retinal changes have been reported.

As a result of two years' experience with some 200 patients we are satisfied that the only side-effects worth mentioning are those associated with the anti-cholinergic properties of Melleril and its effects on the brain stem and pituitary function. We have not seen any cases of depression of liver function and no cases of jaundice have occurred and so far no allergic reactions or water retention has been noticed. In fact we have treated at least one patient who manifested severe allergic reactions with other phenothiazine compounds but tolerated Melleril perfectly satisfactorily. One does not, therefore, anticipate any difficulty resulting from skin rashes or oedema of the tissues.

Amongst the most common side-effects which we have noticed was drowsiness. This depends on the dose given. A few patients complained of it who received 150 mg. daily. Most patients will complain of drowsiness on 300 mg. daily although we have had an occasional patient receiving 400–500 mg. daily who did not complain of this symptom and these were usually patients who were rather severely disturbed mentally. A few patients on long-term treatment who had left hospital gave up taking the tablets on account of drowsiness, although these symptoms can be controlled by dexedrine to some extent. This also has the advantage that it tends to counteract the tendency to gain weight.

Dizziness and faintness due to hypotension sometimes occurred at the beginning of treatment and can usually be avoided by stepping up the dose at weekly intervals. It is not a serious complication.

Next in order of importance was amenorrhoea in the women and perhaps less commonly inadequacy of sexual function in the men. In some groups of patients of child-bearing age the amenorrhoea occurred in up to 50 per cent. of cases, but as these were all schizophrenics it may be partly attributed to the illness itself. Patients in the group receiving long-term treatment tended to menstruate again after about six months although somewhat irregularly. It did not seem to us to be of any clinical importance although some of the patients became anxious about it. In all cases menstrual function returned after we stopped the tablets. In 2 patients lactation occurred and this ceased after diminishing the dose of the tablets.

Other side-effects occasionally complained of were nasal stuffiness and dryness of the mouth. There were, of course, other complaints of disturbances of bodily function but we felt that these were not due to the tablets themselves. No patient complained of visual disturbance and tests showed no changes in the visual fields or of retinal function.

Parkinsonism is a rare symptom. This may be because few of our patients received more than 300 mg. daily although in our opinion it is not necessary to exceed this dose in most cases. It only occurred to any extent in 3 patients, 2 of whom were brothers and who deteriorated mentally as the parkinsonism progressed. This is worthy of comment, as in the past workers with other phenothiazines have felt that treatment is more efficient when parkinsonism is allowed to develop. Four patients who developed disabling parkinsonism on chlorpromazine had none on similar or higher doses of Melleril and at the same time improved mentally.

Dosage

This has already been discussed but will now be summarized. A parenteral form of Melleril is not yet available and all doses refer to oral administration of tablets. In psychosis 150 mg. daily in three doses is a useful commencing dose but in acute cases an initial loading dose of 200 mg. can be given followed by 100 mg. 4 or 6 hourly until control is obtained. In less severe cases the dose may be increased during the second week to 300 mg. daily and in more severe cases may be reduced to this level after a few days. Maintenance doses vary from 75 mg. to 300 mg. daily but 150 mg. daily is the average. It is important to reduce the dose as the patient improves. Psychotics of some duration needing long-term maintenance treatment who have been discharged from hospital require observation and should be seen at first at weekly intervals, extending the time to 4-weekly intervals after 2 or 3 months. In neurotic tension states somewhat lower doses may suffice.

Summary

Melleril or thioridazine is one of a new series of phenothiazine derivatives which is effective in schizophrenia and is believed by the authors to be the most effective high-dose phenothiazine available for the management of the psychoses.

Melleril has been given to 200 psychiatric patients over a period of 2 years. During this period it has proved itself to be safe and to be singularly free from side-effects, particularly extra-pyramidal and allergic complications. Controlled double-blind trials have demonstrated it to be superior to placebo tablets and to its close rival, KS75.

Melleril is most effective in the treatment of acute and subacute schizophrenia and in the management of long-standing paranoid schizophrenia and

paraphrenia. Many of these patients have been able to leave hospital and are leading normal and productive lives on long-term maintenance treatment.

The dose required varies from 300 mg. to 500 mg. daily in the acute case to an average of 150 mg. daily for maintenance treatment.

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BIBLIOGRAPHY

TAESCHLER, M., and CERLETTI, A., "Zur Pharmakologie von Thioridazin, Melleril", *Schweiz. Med. Wschr.*, 1958, **48**, 1216.

Iidem, "Differential analysis of the effects of phenothiazine-tranquillizers on emotional and motor behaviour in experimental animals", *Nature*, 1959, 12 September, 823.

FOULDS, G. A., "Clinical research in psychiatry", *J. Ment. Sci.*, 1958, **104**, 259.

COHEN, S., "TP 21, a new phenothiazine", *Amer. J. Psychiat.*, 1958, **115**, 358.

HOLLISTER, L. E., and MACDONALD, B. F., "Thioridazine (Melleril) in psychiatric patients". Paper presented at annual meeting of California Medical Association; Section on Psychiatry, San Francisco, 25 February, 1959. To be published.

FLEESON, W., GLUECK, B., HEISTAD, G., KING, J. E., LYKKEN, D., MEEKL, P., and MESIA, A., "The ataraxic effect of two phenothiazine drugs on an out-patient population", *Univ. Minnesota Med. Bull.*, 1958, **29**, 274.

KINROSS-WRIGHT, V., "Newer phenothiazine drugs in the treatment of nervous disorders", *J. Amer. Med. Ass.*, 1959, **170**, 1283.