A NEW PERIDOL DERIVATIVE IN THE TREATMENT OF CHRONIC SCHIZOPHRENIA*

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The elderly chronic schizophrenic patient presents a formidable problem to the mental hospital. This has been investigated in Britain,[1] and the problem at Ingutsheni Hospital appears fundamentally similar. A survey of patients in the hospital on 31 December 1967 showed that 282 of 595 male patients (47%) and 94 of 213 female patients (44%) were classified as schizophrenic. Of these schizophrenic patients, 194 males (69%) and 57 females (61%) had been in hospital for 2 years or longer.

The effectiveness of drug therapy (as compared with ECT alone, or psychotherapy alone) has been firmly established[2] but the choice of drug is by no means clear. There have been trials with African patients, e.g. with thioridazine,[3] but remission was not obtained with cases of more than 5 years' standing.

Encouraging results were obtained with a peridol derivative in very chronic African schizophrenic patients who had been in hospital more than 20 years.[4] This drug, FR 33 (Sandoz), seemed to merit further trial.

MATERIALS AND METHODS

Because of difficulties with continuity of staff, only female patients are included. Twenty patients were selected according to the following criteria:

1. A minimum period of 5 years continuously in hospital.
2. An initial diagnosis of schizophrenia on admission.
3. The diagnosis was supported in retrospective review using the generally acceptable criteria set out by Willis and Bannister.[5]

The blood WR was negative in every case, but the EEG proved to be abnormal in 2 patients who were therefore excluded, leaving a total of 18.

All these 18 patients had been treated with various drug combinations, with or without ECT, and none had shown any sustained improvement. Further, the drug had been shown to have a very low toxicity, both in animal experiments and previous unpublished trials. These factors were considered sufficient to render the trial ethically justifiable.

Preliminary information intimated that the effects of the drug would not be manifest until some 2 months' treatment had been completed and that the action of the drug would be sustained for at least 2 months after it had been withdrawn.

The patients were therefore divided at random into 2 groups, an initial treatment group (group A) and an initial placebo group (group B). It was intended that group A should have treatment for 2 months, then change to the placebo for 2 months; group B was intended to begin with 2 months on the placebo, then change to treatment for 2 months. If both hypotheses were correct, group A should have shown improvement at the end of 2 months, sustained at the end of 4 months, and group B should have shown no improvement at the end of 2 months but improvement after 4 months.

Since all patients, with the possible exception of Nos. 1526 and 7574 for whom the early records were incomplete, had had several courses of treatment previously, a double-blind trial was not considered necessary. A 'single-blind' trial was considered adequate (i.e. psychiatric ratings to be done blind but the patients to be aware that they were receiving different tablets although not aware that one was a placebo). It was intended that there should be an initial psychiatric rating, one at 2 months and one at 4 months.

The scale selected was designed for use during a brief interview and to give an index of the degree of 'psychoticness'.[6] For the purposes of this investigation the last category 'Judgement and abstracting ability' was omitted as it was considered that language difficulties would preclude any accurate assessment. In addition to the psychiatric rating scale, a ward behaviour scale was completed by the nursing staff at weekly intervals. The scale used was that designed for use at Mohlomi Hospital, Lesotho,[7] and is particularly suitable for African patients.

The patients were randomly divided into two groups of 9. With certain exceptions discussed below, the composition of the groups was not revealed to the investigators until after the completion of the trial.

Conduct of the Trial

The trial commenced in December 1965. During this month all patients were assessed on the psychiatric rating scale by two investigators working separately. Comparison of results revealed that the inter-rater reliability was not very high. This was partly due to conceptual difficulties, in particular that of rating the patient with poverty of ideation since the scale did not contain a category corresponding with 'negative formal thought disorder'.[8]

These difficulties were resolved and all patients were then rated by both investigators working in conjunction. On this occasion only were the results of the previous rating available to the investigators; at all other ratings a fresh rating sheet was used to eliminate the effect of 'runs'.[9]

*Date received: 19 July 1968.

The first ward behaviour rating was completed on 1 January, and on 3 January group A commenced FR 33 10 mg. *t.d.s.* and group B tabs. Vit. B Co. 1 *t.d.s.* Vitamin supplements may cause psychiatric improvement,[10] but this was not considered a significant factor.

Contrary to expectation the nursing staff reported considerable behavioural changes in patients in the treatment group towards the end of the first month of the trial. In order to allow for this, the design of the trial was altered so that patients changed from treatment to placebo and vice versa at the end of 1 month. Unfortunately, owing to the absence on leave of one of the investigators it was not possible to obtain a psychiatric rating at this stage, but ward behaviour ratings were continued at weekly intervals throughout. No change was observed in the placebo group. After this change at the end of 1 month, the original trial design was followed. That is, medication was as follows:

Group A.	FR 33	10 mg. *t.d.s.* for 1 month
	Vit. B Co.	tabs. 1 *t.d.s.* for 2 months
	FR 33	10 mg. *t.d.s.* for 2 months
Group B.	Vit. B Co.	tabs. 1 *t.d.s.* for 1 month
	FR 33	10 mg. *t.d.s.* for 2 months
	Vit. B Co.	tabs. 1 *t.d.s.* for 2 months

Psychiatric ratings were completed on all patients initially, and after 2, 3 and 4 months.

Ward behaviour ratings were completed on all patients at weekly intervals throughout.

This pattern is set out in Fig. 1.

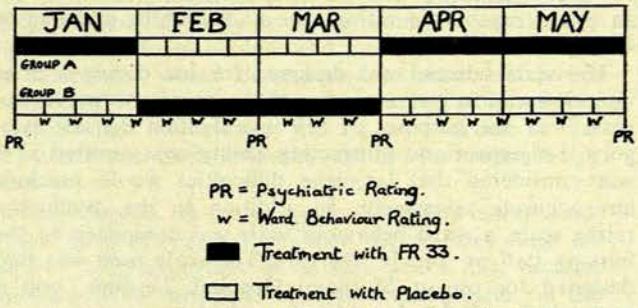

Fig. 1. Pattern of ward behaviour ratings.

RESULTS

Side-effects of FR 33

In a previous unpublished trial of FR 33 in South Africa, 4 out of 29 patients showed pre-collapse symptoms with fall in blood pressure, sweating, nausea and vomiting. Although the dosage in the present trial was much lower (30 mg. daily as opposed to 50 mg.), daily blood pressure records were kept by the nursing staff for patients on this drug.

In group A, 2 patients showed a fall in blood pressure of sufficient magnitude to warrant reduction of dosage. In both cases the drug was withheld for 48 hours until the systolic pressure had recovered to 100 mm.Hg; treatment was then recommenced with 10 mg. *b.d.* One patient subsequently died, and in the second leg of the trial the surviving patient showed a transient fall in pressure a few days after starting treatment, but she recovered spontaneously without reduction of dosage.

A further patient in group A contracted a brief febrile illness. Her FR 33 was omitted for 48 hours in case there should be any interference with antibody formation, but she rapidly recovered and was given the full dosage for the remainder of the month.

The code was broken for these 3 patients.

Psychiatric Changes in Response to FR 33

The compilers of the Psychiatric Rating Scale considered that one of the most meaningful ways of using the scale was to take the whole scale score as an index of 'psychoticness'. The scale was used in this way and the scores given are raw whole scale scores; the various correcting factors were not applied since these would not have affected the scores significantly and would have implied an unjustified degree of clinical accuracy.

Comparison of the first two scores for each patient suggested that rate/rerate variation was not likely to have been a significant factor.

Since symptoms were given both positive and negative signs, improvement was indicated by regression towards zero; that is, an increase in the numerical value of a score, whether of positive or negative sign, indicated a deterioration.

The ward behaviour rating scale did not have numerical values attached to the behavioural categories, and for this reason it was difficult to arrive at a global assessment of the degree of illness. However, the over-all impressions of the ward-sister provided valuable information of this kind, while the ward behaviour rating scale assessments illuminated changes in particular symptom groups.

In general there was a surprisingly close correlation between all three methods of assessment. The psychiatric rating scale scores are set out in Tables I and II for groups A and B, respectively.

TABLE I. PSYCHIATRIC RATING SCALE SCORES FOR GROUP A

Patient's No.	*Date of rating*					*Result of treatment with FR 33*
	16/12/65	*28/12/65*	*3/3/66*	*4/4/66*	*2/6/66*	
12091	+ 6	+ 7	+ 9	+14	+ 5	Deteriorated
7116	+26	+23	+13	+17	+18	Improved
7574	+17	+17				Died 6/2/66
11416	+ 8	+ 8	− 6	− 5		Died 31/5/66
7561	+ 8	+ 8	− 1	− 5	−27	Deteriorated
9350	+ 7	+ 7	0	+11	+ 4	Deteriorated
6426	+10	+10	+ 2	+ 3	+11	Unchanged
9955	+ 1	+ 3	+ 4	+ 7	+ 3	Unchanged
8412	+ 3	+ 6	+63	+17	− 2	Deteriorated

TABLE II. PSYCHIATRIC RATING SCALES FOR GROUP B

Patient's No.	*Date of rating*					*Result of treatment with FR 33*
	16/12/65	*28/12/65*	*3/3/66*	*4/4/66*	*2/6/66*	
4017	+ 4	− 4	+ 5	+ 9	+18	Deteriorated
11099	+15	+15	+11	+ 9	+ 6	Improved
13679	+15	+19	+ 3	+ 8	+29	Improvement then relapse
12029	+ 1	+18	− 2	+14	+ 6	Unchanged
9527	+ 3	+ 9	+ 2	+ 2	+ 9	Unchanged
1526	+ 5	+ 7	− 5	−14	−17	Deteriorated
1351	+36	+36	+24	+31	+22	Deteriorated
7497	+ 4	+ 7	+ 8	+ 5	+ 1	Unchanged
7342	+ 9	+ 9	−9	+23		Died 19/4/66

There were no essential differences between the two groups, and the patients' responses to FR 33 may be summarized as: improved 3, unchanged 5, and deteriorated 10 (3 died).

Patients who improved. The predominant symptom patterns of the 3 patients who improved were, respectively:

thought disorder with hallucinations, and disorientation; withdrawal and blunting of affect; and delusions and auditory hallucinations.

All 3 showed some improvement in the first month, but the third patient subsequently showed reactivation of her delusions and hallucinations in a more fulminating and bizarre form.

Patients who deteriorated. Of the 10 patients who deteriorated, one had presented with disconnected thinking, hallucinations and inappropriately elated affect on admission, subsequently lapsing into generally withdrawn behaviour with occasional aggressive and destructive outbursts. The FR 33 seemed to reactivate her delusions and hallucinations and make her extremely overactive and aggressive.

Thought disorder, present on admission, was reactivated by FR 33 in 3 other patients. This reactivation of symptoms was also noted in an unpublished South African trial.

Three other patients in this group presented rather different pictures. One showed an initial change to overactivity but became withdrawn and indolent after 2 months' treatment. Another, who had been quiet, unoccupied and unresponsive, became hallucinated and grossly overactive (singing and dancing); her score actually showed a marginal improvement. The third patient showed reduction of motor activity, facial expression and amount of involvement with the examiner despite symptoms of thought disorder with delusions and voluble disconnected speech on admission.

Three patients died and postmortem examinations were made in each case. Although none of the deaths could be directly attributed to the drug, and deaths are more common in the winter months, it is possible that the induced overactivity was a contributory factor. One died from pulmonary tuberculosis after a brief illness lasting 3 days. Another died from congestive failure due to myocardial atrophy, and it is interesting to note that one South African worker recorded a sudden death due to 'cardiac dilatation' after FR 33 300 mg. daily for several weeks.[4] The third patient died from bronchopneumonia but there was evidence of myocardial damage.

CONCLUSIONS

The action of FR 33 seems to be highly complex. Patients may improve, either by becoming 'activated' or by reduction of symptoms such as thought disorder, hallucinations and delusions. Patients may deteriorate, and again the deterioration may be in the form of reduced activity and withdrawal or in the reactivation of hallucinations, delusions and thought disorder or motor activity.

The reaction of the patient seems to depend to some extent on the initial type of schizophrenia.

SUMMARY

A new peridol derivative was tried in the treatment of 18 selected chronic female African schizophrenic patients.

A single-blind, cross-over design was used; the trial extended over 5 months. Psychiatric ratings, ward behaviour ratings and subjective reports by ward-sisters were used to assess progress; all three showed general agreement.

The actions of the drug proved to be complex, but a notable feature was the reactivation of motor activity and symptoms of thought disorder. To some extent the response to the drug seemed to depend upon the clinical picture before the onset of schizophrenic deterioration.

Only 3 patients were rated as improved, and the drug was not considered suitable for general use, but might be of value in selected cases, possibly in conjunction with phenothiazine.

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