A COMPARISON OF TETRABENAZINE AND CHLORPROMAZINE IN CHRONIC SCHIZOPHRENIA

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At the present time only two groups of drugs have an established place in the treatment of chronic schizophrenia, the phenothiazine derivatives and the rauwolfia group of alkaloids. Of these two groups the phenothiazines are in more general use, and, although not free from side-effects, are safer drugs for the long-term management of schizophrenic patients. They also have a wider range of effectiveness in the different schizophrenic syndromes. Many observers, however, have been impressed by the dramatic results obtained in a proportion of cases of long-term schizophrenia treated with the rauwolfia alkaloids and these may be effective in cases not responding to the phenothiazines (Kline, 2).

Tetrabenazine is a new drug of considerable theoretical interest.

It is a benzoquinolizine derivative and its pharmacological properties have been described in detail by Quinn et al. (4). Its effects in producing sedation in the experimental animal are similar to those of reserpine. After a single injection of tetrabenazine there is a fall in the concentrations of 5-hydroxytryptamine

* This work was carried out when the first and third authors were registrars in the Craig House section of the Royal Edinburgh Hospital.
and catecholamines in the brain and an increased excretion of 5-hydroxyindolyl-3-acetic acid in the urine. The sedative effect of the drug closely parallels in time the depletion of brain amines. The brain hydroxytryptamine concentration returns to normal within twenty-four hours whereas in the reserpine-treated animal it remains depressed for six to seven days. If administration of tetrabenazine is preceded by premedication with iproniazid the animal becomes excited and the brain 5-hydroxytryptamine shows only a slight decline.

Clinical trials of tetrabenazine have been carried out by Voelkel and Dresler (5) and Lingjaerde (3). These workers report improvement in chronic schizophrenic patients and did not encounter serious side-effects. An important point which has emerged from both experimental and clinical studies is that cardiovascular complications such as the bradycardia and hypotension produced by reserpine do not occur. This may be because tetrabenazine, unlike reserpine, does not reduce the concentration of noradrenaline in peripheral tissues (Quinn et al., 4).

We report here a controlled trial of tetrabenazine in the treatment of chronic schizophrenic patients. The trial was designed to obtain answers to the following questions. (a) Does the drug compare favourably with chlorpromazine, a standard treatment in this type of patient? (b) What is its range of usefulness? (c) What are the side-effects? In order to answer these questions as comprehensively as possible a wide range of chronic schizophrenic patients, classified according to principal symptoms, was chosen. Several elderly patients were included in order to assess the safety of the drug in this age group.

**The Clinical Trial**

Fifty-two long-term female schizophrenic patients, duration of illness three to thirty-four years, from five wards of the hospital, were chosen for the trial.

They were divided into two groups by a colleague whose only other role in the trial was the dispensing of the drugs. The groups were matched by him for age, clinical assessment, behaviour rating on the scale of Baker and Thorpe (1) and previous leucotomy.

Each group contained 26 female patients. The mean age in the tetrabenazine group was 56·1 (standard deviation 12·8). The mean age in the chlorpromazine group was 58·3 (standard deviation 11·0). Four patients in each group had had a previous leucotomy. The mean initial behaviour rating scores were not significantly different in the two groups, being 82·3 (standard deviation 39·7) in the tetrabenazine group and 82·5 (standard deviation 38·6) in the chlorpromazine group.

Neither the authors nor the nurses knew to which group the patients had been allotted, until completion of the trial. Supplies of matching capsules were obtained containing chlorpromazine 75 mg. or tetrabenazine 30 mg. or an inert placebo. The patients were studied for twenty weeks, the trial period being divided into three stages:

1. **First six weeks.** All day-time medication was discontinued at the start of this period except in three patients who required a sedative of sodium amytal 200 mg. t.i.d. on account of disturbed behaviour. Night sedation was standardized; when a sedative was required sodium amytal 200 mg. was prescribed. In all other respects the ward routine was continued as usual. At the beginning of the sixth week the nursing staff began to fill in daily behaviour rating charts for each patient.
Seyventh and eighth weeks. During these weeks one placebo capsule was administered three times daily to all patients in the trial.

Ninth to twentieth weeks. The patients received either tetrabenazine or chlorpromazine according to the group to which they had been allocated. For the first four weeks of active treatment (weeks 9 to 12) one capsule three times daily was administered and for the last eight weeks (weeks 13 to 20) one capsule four times daily. Thus the patients received tetrabenazine 90 mg. or chlorpromazine 225 mg. daily for four weeks and then tetrabenazine 120 mg. or chlorpromazine 300 mg. for eight weeks.

Assessment

The mental state was assessed by two methods.

Clinical Examination

A detailed mental examination was carried out during the placebo period and during the twentieth week of the trial. Each patient was interviewed by the same doctor on both occasions. At the first interview the following psychotic symptoms were especially sought; disorder of affect, thought disorder, hallucinations, delusions, ideas of reference and catatonic signs. The information obtained was utilized by the colleague who divided the patients into two groups. On re-assessment at the second interview, the patients were rated as definitely improved, no change or worse. Any marked change in one symptom, e.g. thought disorder, was also noted.

Behaviour Rating

From the beginning of week 6 each patient was assessed daily by the nurse-in-charge on ten items according to the behaviour rating scales of Baker and Thorpe (1). The rating scale scores were used to measure two aspects of behaviour as described by Baker and Thorpe, viz.:

(a) Schizophrenic Deterioration. This was measured by the sum of the ratings of the ten scale items. The daily marks for the ten items on the scale were added together to give a weekly score for each patient.

(b) Restlessness. The sum of the weekly totals for two items in the scale, viz., day and night restlessness, were used as a measure of psychomotor restlessness.

Physical Examinations

These were carried out by one of the authors (E.M.) during weeks 6 and 20. Pulse rate, blood pressure and E.S.R. were recorded.

Results

Six patients in the tetrabenazine group and two patients in the chlorpromazine group failed to complete the trial. Of the former, one was withdrawn because of the objection of a relative and five because of side-effects which are described below. One patient in the chlorpromazine group had a cerebral thrombosis during the seventh week of the trial, when receiving the placebo, and another absconded from the hospital during the fourth week of the trial.
COMPARISON OF TETRABENAZINE AND CHLORPROMAZINE

BEHAVIOUR RATINGS

Schizophrenic Deterioration

Table I

<table>
<thead>
<tr>
<th>No. of Patients Completing Trial</th>
<th>Week 6 Treatment</th>
<th>Week 20 Treatment</th>
<th>Significance of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrabenazine</td>
<td>20</td>
<td>82.4±40.1*</td>
<td>62.6±33.6</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>24</td>
<td>85.1±42.2</td>
<td>56.3±35.4</td>
</tr>
</tbody>
</table>

*±standard deviation

There was a significant improvement in the mean rating scores during the trial in both groups. The trend was for the chlorpromazine group to improve more than the tetrabenazine group but the difference was not statistically significant.

Table II

<table>
<thead>
<tr>
<th>No. of Patients Completing Trial</th>
<th>Week 6</th>
<th>Week 20</th>
<th>Significance of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrabenazine</td>
<td>20</td>
<td>8.2±4.4*</td>
<td>5.7±5.5</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>24</td>
<td>10.8±1.1</td>
<td>4.5±5.7</td>
</tr>
</tbody>
</table>

*±standard deviation

There was no significant change in the mean restlessness scores of the tetrabenazine patients but there was a significant improvement in the scores of the chlorpromazine group.

It was also our clinical impression that psychomotor over-activity was better controlled in those patients who later proved to have been receiving chlorpromazine.

An analysis of the results as assessed at clinical interview can be summarized as follows. Twenty-four patients in the chlorpromazine group and twenty in the tetrabenazine group completed the trial. Six patients receiving chlorpromazine showed definite improvement, one deteriorated and seventeen showed no change. Of the tetrabenazine group, seven showed definite improvement, one deteriorated and twelve did not change.

An analysis of the improvement in the main symptoms reveals the following picture (Table III).

Table III

Analysis of Improvement in Individual Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Thought Disorder</th>
<th>Catatonic Signs</th>
<th>Paranoid Symptoms</th>
<th>Affective Disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

These numbers are too small for valid statistical analysis, but the improvement in thought disorder in some of the patients receiving tetrabenazine was very marked; this is illustrated by the following case history:
Case

A married woman, aged 58, had been in hospital for fourteen years. At the start of the drug trial she was withdrawn and showed marked affective blunting, auditory hallucinations and a very gross thought disorder. Asked how she was, she replied, "Why do we have to see an engine?" and then said, "How's your toothache?" By the end of the trial it was possible to carry on a fairly normal conversation with her, and to the above question, she replied, "I'm feeling very fit, thank you. What was wrong when I was brought here?" She admitted to auditory hallucinations but subsequently (tetrabenazine having been continued) these ceased and it is now difficult to detect any abnormality in her stream of thought. She still shows affective blunting, however, and retains certain delusions, but continues to improve slowly.

Physical Effects

Table IV shows a comparison of blood pressure, pulse rate and E.S.R. before and after the trial. The blood pressures and pulse rates were recorded when the patients had been at rest in bed for thirty minutes.

| TABLE IV |
| Mean Readings and Standard Errors of Blood Pressure, Pulse Rate and E.S.R. Before and After the Trial |
| 6th Week | 20th Week | P  
| Tetrabenazine: |
| Systolic blood pressure | 149.3±6.4* | 138.3±7.3 | >0.05  
| Diastolic blood pressure | 88.5±3.4 | 78.0±3.7 | <0.05  
| Pulse rate | 77.5±0.2 | 77.0±5.7 | <0.05  
| E.S.R. | 17.6±8.4 | 22.3±8.4 | >0.05  
| Chlorpromazine: |
| Systolic blood pressure | 152.9±5.7 | 135.0±5.4 | <0.05  
| Diastolic blood pressure | 88.9±7.9 | 77.5±6.0 | <0.001  
| Pulse rate | 76.9±1.4 | 84.0±5.9 | <0.01  
| E.S.R. | 17.9±7.1 | 26.7±4.1 | >0.05  

*±standard deviation

In the tetrabenazine group the only significant change was a fall in diastolic blood pressure, whilst in the chlorpromazine groups both diastolic and systolic blood pressure showed a fall and the pulse rate a significant increase.

SIDE-EFFECTS

These were most troublesome in the tetrabenazine group, five of these patients being withdrawn because of severe side-effects. Of the five, two developed a subacute delirium, one a generalized tremor, one marked unreality feelings and agitation, and one became suicidally depressed. The side-effects which were not severe enough to necessitate withdrawal from the trial were as follows. In the tetrabenazine group, one patient developed a recurrent catatonic stupor, one a Parkinsonian syndrome, two became extremely drowsy during the first week of therapy and four showed severe motor restlessness. In the chlorpromazine group, four patients developed Parkinsonism, four showed drowsiness in the early stages of treatment and one developed a severe fine tremor of the hands.

The side-effects in the chlorpromazine group are consistent with previous reports.

The side-effects in the tetrabenazine group call for a more detailed description.
1. Subacute delirium. Two patients, aged 79 and 78 (the eldest two in the trial) developed a subacute delirious state with clouding of consciousness, restlessness, particularly at night, and in one case incontinence. These symptoms came on during the first week of treatment and it was necessary to discontinue the drug, when they disappeared within twenty-four hours.

2. Severe motor restlessness appearing within a week of commencing the drug was apparent in four catatonic patients who had previously shown little activity.

3. Catatonic stupor.
Case 2
A 62-year-old patient, who had been in hospital for eleven years, showed a peculiar transition to a periodic type of catatonic syndrome when started on tetrabenazine. Before the trial she spent most of the day sitting in one position and her gross thought disorder only rarely emerged in speech. On the second day of tetrabenazine treatment she lapsed into catatonic stupor. During the next six weeks, episodes of stupor lasting two to three days alternated with periods of near normality of approximately one week's duration. During the last six weeks of the trial, however, the periodicity disappeared and her condition returned to a state little better than the pre-treatment level.

4. An extra-pyramidal syndrome of Parkinsonian type with tremor, rigidity and mask-like facies but without sialorrhoea was seen in one patient (Case 1).

5. Depression. One patient in the tetrabenazine group became depressed during the trial.
Case 3
A single woman, aged 76, with a schizophrenic illness of thirty-two years' duration, had a history of depressive symptoms in 1938 but these had not since been a feature of her illness. During the fifth week of tetrabenazine treatment she developed a typical depression with retardation and suicidal thoughts. The tetrabenazine was discontinued but she remained extremely depressed expressing the belief that her internal organs had ceased to function and that there was no hope for her. After four weeks she was given a course of seven electro-plexy treatments and the depression cleared. She reverted to her previous hallucinatory schizophrenic state.

6. Impulsive suicidal attempt.
Case 4
A single woman, aged 36, with a schizophrenic illness of twelve years standing appeared to be improving when she suddenly attempted suicide by throwing herself over a bannister. This act appears to have resulted from her awareness of her position in a long-stay ward with other chronic patients. She was not injured and there was no repetition of this impulsive behaviour. The tetrabenazine was discontinued, however, and she was transferred to another ward.

DISCUSSION

We can now attempt to answer the questions posed at the start of the trial.

1. The results of the trial suggest that tetrabenazine, like chlorpromazine, is of value in the treatment of chronic schizophrenia.

2. Where restlessness and over-activity are prominent features, chlorpromazine is superior to tetrabenazine, but the latter drug is of particular value in cases where thought disorder dominates the clinical picture.

3. Side-effects of tetrabenazine are more numerous than those of chlorpromazine but the former drug is free from the cardiovascular complications of reserpine therapy. All side-effects, with the exception of depression, subside within 24 hours on discontinuation of treatment.

The development of depression during administration of tetrabenazine suggests that the drug may share with reserpine the potentiality of producing a depressive state and that it should therefore be used with caution in cases of
schizophrenia showing a strong affective component. The depression in our case responded rapidly to electroplexy when it had failed to resolve spontaneously. It is of interest to record here that Lingjaerde (3) and Voelkel and Dresler (5) found that tetrabenazine causes no prolongation of the apnoeic phase after electroplexy therapy and state that the two treatments may be used concurrently.

The motor restlessness and agitation seen in some of our tetrabenazine-treated cases may be analogous to the turbulent phase sometimes seen during the early stages of reserpine therapy.

We consider that tetrabenazine has a place in the treatment of patients with long-standing schizophrenia, particularly those who have responded little (or not at all) to the phenothiazines. It seems to be of particular value in the amelioration of the symptom of thought disorder. The number in our trial is small and it must be regarded as a pilot study. We feel that further studies are required to amplify the information so far available. In particular a trial of the drug in acute schizophrenia would appear to be a logical development.

It is of particular interest to note that the possible clinical usefulness of tetrabenazine was deduced from a knowledge of its biochemical and pharmacological action in animal studies. It is to be hoped that the development and study of the actions of this and other new psychotropic drugs will lead to further advances in the elucidation of the aetiology of the psychoses.

SUMMARY

1. A controlled trial was carried out to compare the efficacy of tetrabenazine with that of chlorpromazine in chronic schizophrenia. Fifty-two female patients in two matched groups were studied over a period of twenty weeks.

2. Both groups of patients showed significant improvement during treatment. The trend was for chlorpromazine to be more active in controlling psychomotor over-activity and for tetrabenazine to be particularly effective in lessening thought disorder.

3. Although side-effects caused suspension of treatment in five patients in the tetrabenazine group, the drug may be safely administered to patients in hospital and appears to be worthy of more extensive trial.

ACKNOWLEDGMENTS

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REFERENCES