AN INVESTIGATION INTO THE EFFECTS OF AZACYCLONAL ON THE HALLUCINATIONS OF CHRONIC SCHIZOPHRENIC PATIENTS

By

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FRENQUEL, α-(4-piperidyl) benzhydrol hydrochloride, generically known as Azacyclonal hydrochloride was introduced commercially into this country in the early part of 1957 although it had already been available in the United States of America for several months previously. Sargant (1956) obtained a supply of Azacyclonal from America and in his paper on Chemical Tranquillizers he refers to Azacyclonal as "an interesting drug". Azacyclonal was thought to be the first drug to possess a specific anti-hallucinatory effect.

Fabing (1955) was the first to acclaim the unusual properties of Azacyclonal when he found that it relieved the confusion and hallucinations of a normal healthy student who had previously been given a dose of lysergic acid diethylamide (LSD-25). The actions of LSD-25 other than hallucinogenic were not affected by the Azacyclonal. These observations prompted a number of further investigations and in 1955 and 1956, several reports of the actions and properties of Azacyclonal appeared in American medical literature. Brown *et al.* (1955) carried out pharmacological tests with Azacyclonal and found that it was mildly depressant in low doses and stimulant in large doses. They also found it had little or no effect on the blood pressure and electrocardiograph in the anaesthetized dog although both the rate and depth of respiration increased. Bettag *et al.* (1955) compared the effects of Azacyclonal, reserpine and chlorpromazine on the cerebral electrical activity of rabbits. Azacyclonal had no effect on the electrical activity of a "normal" brain but it corrected the abnormalities produced by LSD-25 or mescaline.

On the clinical side Fabing and Hawkins (1955) reported the results after a year's experience with the drug. They treated 115 patients altogether and found the responses encouraging but variable from patient to patient. Rinaldi *et al.* (1955) treated 39 chronic patients and found significant improvement in a large proportion of them.

Proctor and Odland (1956) treated three different groups of patients. One group consisted of acute patients, in whom the response was good. The second group were chronic patients and here the results were less satisfactory. The third group all had toxic psychoses, mainly brought about by alcohol, and the improvement which followed administration of Azacyclonal was in some cases dramatic. Ferguson (1956) tried Azacyclonal in 264 chronic female patients and noticed changes in behaviour in a number of them. The results obtained by different workers who have used Azacyclonal and the dosages recommended vary considerably and the only observation which is common to all reports is the complete absence of side-effects which accompanies Azacyclonal therapy.

In view of these findings it was decided to determine the effect of Azacyclonal on the hallucinations of a number of chronic patients.

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Clinical Material

The patients chosen for the trial were all women selected from three chronic wards. The duration of their stay in hospital varied from eight to thirty-nine years, averaging 18·33 years. Fifty patients were selected but during the trial four of them, for various reasons, had to be excluded. All were markedly disturbed and all suffered particularly from auditory hallucinations which had not been affected by previous therapy.

Methods Used

The patients were divided into two groups (A and B) and matched for age (Table I) and severity of symptoms. The method of arriving at the severity rating is explained in Table II.

Table I

Group A				Group B			
Severity	Age	Severity	Age	Severity	Age	Severity	Age
9	74	7	56	11	71	9	57
7	73	11	51	9	72	11	52
8	69	11	58	7	66	10	51
10	69	10	57	10	68	7	58
10	68	9	49	9	67	11	47
9	62	7	43	9	64	7	44
8	59	5	44	8	63	6	47
6	61	8	46	5	60	8	47
7	63	8	37	7	64	6	33
8	65	8	56	8	62	10	53
6	52	7	60	4	59	7	64
7	56	9	49	8	59	10	44
		9	63			8	64
Mean 8·16		Age 57·6		Mean 8·2		Age 57·44	

The duration of the trial was three months. During the first half of the trial Group A received placebo tablets and Group B those containing the active preparation. The pattern of administration was then reversed, Group A receiving the active preparation and Group B control tablets. After the first six weeks there was a four-day interval when both Azacyclonal and placebo therapy were withdrawn. The second half was then run exactly as the first but with the administration of placebo and active material reversed. The double blind technique was used. Throughout the trial only the pharmacist knew which patients were receiving the active preparation and which were receiving placebo. The key was not revealed until the termination of the trial.

Laboratory investigations included haemoglobin determinations, white cell counts and blood sedimentation rates. These were carried out weekly with each patient for a total of thirteen weeks in each case. No significant change was noticed in any patient and it was therefore considered unnecessary to investigate the blood picture further. No autonomic side-effects or any other toxic effects were observed clinically. The severity rating of each patient was calculated (as in Table II), before the trial commenced and at the end of the first and last halves. In addition day to day assessments were made by the observers and any change carefully noted.

TABLE II

	Sister	Sister	Doctor	Doctor	
	Frequency of Hallucination	Response to Hallucination	Reality Basis of Hallucination	Degree of Insight	Severity Rating
I					
II					
III					

Frequency:

Hallucinations noticed once or twice during day = 1
Hallucinations noticed several times during day = 2
Hallucinations noticed very frequently or continuously = 3

Response to Hallucinations:

Attending = 1
Answering and responding = 2
Answering and responding violently = 3

Severity Rating: This was taken as the sum of the points allotted to each patient in the four columns of the table.

Reality Basis:

Mainly rational = 1
Mainly irrational = 2
Bizarre = 3

Insight:

Some = 1
Little = 2
None = 3

Mean:

Group A — 8·16
Group B — 8·2

DOSAGE

The initial daily dose of Azacyclonal was 60 mg. and every fourth day this was increased by a further 60 mg. up to a maximum of 420 mg. daily given in three equally divided doses. To avoid unnecessary complications only the oral form of Azacyclonal was employed. Any other treatment the patients were receiving was continued during the course of the trial.

RESULTS

With doses less than 300 mg. daily little or no effect was apparent in any patient. When a dosage of 300 mg. daily was reached, it was noted that a percentage of the patients improved from a social point of view, although the hallucinations were not specifically influenced. As the original purpose of the trial was to assess the anti-hallucinatory effect of Azacyclonal no provision had been made on the assessment tables for any change in social behaviour to be noted. It is therefore not possible to present a statistical analysis of these changes. Both active and control material produced this effect.

These improvements included:

1. A better social contact and an ability to converse with other patients.
2. Sufficient responsibility to be allowed ground parole.

3. Better attention to personal hygiene with a subsequent reduction in nursing supervision.
4. Ability to do light domestic work in the ward.

Observations have indicated that the above improvements were slightly more apparent on patients receiving the placebo preparation as opposed to the active drug. Of the 46 patients, 7 became noisier and appeared to deteriorate whilst on active material.

Since hallucinations were not affected in any way, statistical analysis was not considered worth while.

Discussion

Originally this controlled experiment was designed only to determine the effects of Azacyclonal on auditory hallucinations in chronic patients. In each case it is of significance that the hallucinations had been present for many years and had not responded to previous therapy. As some confusion exists about the optimum dosage of this drug an attempt was made to clarify the position. Four days were allowed for assessment at each dose level. The literature indicated that 300 mg. daily was a reasonable dose, but as this was by no means proven, it was decided to increase the dose to 420 mg. Below 300 mg. daily no clinical effect was observed.

It is disappointing that the results obtained indicate that Azacyclonal is of little or no value in chronic hallucinated patients.

It is noteworthy that three patients each suffering from hallucinations during the acute initial stages of mental illness were treated with Azacyclonal on a dosage of 240–300 mg. daily. The impression gained was that they had improved considerably. This would support the findings of Proctor and Odland (1956).

The social improvement mentioned may well have been due to the fact that more attention was being paid to the patients, and that they were receiving a new treatment.

Summary

An attempt has been made to evaluate Azacyclonal in fifty chronically hallucinated female patients. The dosages used varied from 60 to 420 mg. a day in order to find the dose level producing the maximum therapeutic effect.

Observations in this trial indicate that the average optimum dose is in the region of 300 mg. daily. No side-effects whatsoever were recorded even when 420 mg. daily were given despite thorough laboratory examinations. On the basis of the effect on chronic hallucinations it must be admitted that the results of the trial are disappointing, and it would appear that Azacyclonal is of no value in the treatment of this kind of patient. It is significant that a small number of patients with acute hallucinations have responded dramatically to treatment with Azacyclonal.

If enough clinical material could be accumulated a trial of this drug on acutely hallucinated patients might produce very interesting results.

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