# A CONTROLLED INVESTIGATION OF THE EFFECTS OF CYCLIZINE HYDROCHLORIDE IN CHRONIC PSYCHOSIS

By

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## INTRODUCTION

CYCLIZINE hydrochloride (1-benzhydryl-4-methylpiperazine monohydrochloride) is a popular remedy for motion-sickness. The success which is reputed to attend the use of the drug in this condition may be a function of of two distinct effects: (*a*) a direct, specific inhibition of the vestibular mechanism; (*b*) a general, central inhibition or sedation. A consideration of the latter, rather than the former, suggested the possibility that cyclizine might prove to be of value as a potential "tranquillizer". A controlled clinical trial was carried out in order to establish whether any tranquillizing effects might be associated with the use of the drug in a number of chronic psychotics, all of whom manifested some gross disturbance of behaviour. This paper describes the experimental method which was used; the results which were obtained; and a general comment upon the possible implications of the results in relation to other drugs used in psychiatry.

## METHOD

The object of the trial was to establish whether cyclizine is a potential tranquillizer. A necessary preliminary requirement to the resolution of this problem was to have a satisfactory set of criteria by which the tranquillizing properties of the drug were to be judged. It was necessary, therefore, for the purposes of our investigation that we should select, albeit somewhat arbitrarily, certain criteria by which a fair and reasonable judgment might be made as to the tranquillizing properties of cyclizine. To resolve this difficulty the hypothesis was postulated that if cyclizine is a tranquillizer then it might be expected to modify favourably the behaviour, and perhaps the total clinical picture, of certain patients who objectively may be seen to be in a state very far removed from what might be described as tranquil. The patients we selected to test this hypothesis were chronic deteriorated schizophrenic psychotics, all of whom clearly displayed some visible form of abnormal behaviour or activity. The most disturbed male ward in the hospital was chosen as that portion of the patient population most likely to furnish the required patient material. From a total of 90 patients in this ward, 30 patients were finally selected for inclusion in the trial. They were considered, by the nursing and medical staff alike, to

be the most disturbed patients in the ward, all of whom were known to be restless, noisy, or aggressive.

The next requirement was to decide upon suitable standards by which, during the course of the trial, a change, for better or worse, in the behaviour and clinical state of the individual patient might be validly recorded. This, in turn, entailed the need for the selection of a variety of observations to be made during the trial which would incorporate the required standards for determining change in the patients, and, in consequence, test the tranquillizing properties of cyclizine. Three basic types of observation were selected as those which, in conjunction, would prove most likely to provide an objective and comprehensive judgment or standard of change in the trial patients. These three different types of observations were to comprise: (*a*) the numerical scoring upon a 4 point—23 item psychiatric rating scale; (*b*) the recording of global or conventional clinical judgments; (*c*) the registration of abnormal incidents on behaviour charts.

(*a*) The rating scale was specially designed for the trial, and covered a wide range of symptomatic abnormalities relating to the function of intellect, emotion, and behaviour. The scale was so constituted that a high total score, recorded for a particular patient, would represent gross abnormality; and, conversely, a low score would indicate relatively slight deviation from the so-called "normal". A reduction in the initial score of a patient on the scale, during the course of treatment, would be taken to imply a therapeutic gain; an increase in the initial score representing a deterioration. For convenience, and for the purposes of the final analysis of the results, the difference between a patient's initial and subsequent score was to be designated his "improvement" score. A reduction in his initial score would provide a positive "improvement" score; an increase would yield a negative "improvement" score.

The initial and subsequent ratings were to be carried out by the two investigators (F. and C.); each of whom would act as his own control by retaining the same 15 patients, allocated to him at random, for rating purposes throughout the trial. However, in order to test the validity of the scale to some extent in advance, and to see if a consistency obtained in the ratings of the two investigators, 10 patients, other than those included in the trial but similar in symptomatology, were independently rated by both F. and C. The correlation coefficients, which were found to obtain between the two raters, were of a high order of significance.

(*i*) Product-moment, $r=0\cdot85$, with df. 8, $P=<0\cdot01$. Significant at the 1 per cent. level of confidence.

(*ii*) Rank difference, $rho=0\cdot89$. Standard error$=0\cdot33$. Significant at the 1 per cent. level of confidence.

("Significance" at the 1 per cent. level, in this context, indicates that a consistency as great as that observed to obtain between the two raters, would be expected to occur only once in a hundred repetitions of the ratings, upon the basis of pure chance alone. The conclusion which may be drawn from the P values obtained, and their 1 per cent. confidence levels, is that the two raters obtained a high degree of consistency in their ratings and that, therefore, there is some presumptive evidence that the rating scale itself was really measuring with some degree of reliability.)

(*b*) The global or conventional clinical judgments, which were recorded throughout the trial, were made by the two investigators, upon the same 15 patients assigned to each for rating purposes. These judgments were made without

the previous rating scale scores, or assessments, being available at the time to the investigator, in the interests of the independence and objectivity of the various observations being made. The global assessments were to be based upon 5 discrete categories of overall clinical response, namely: Great improvement; Moderate improvement; Slight improvement; No change; Worse.

(*c*) The behaviour charts were to form a daily record, kept by the nursing staff, of all the noisy outbursts, aggressive acts, and incidents of incontinence and insomnia of each of the patients during the trial.

Certain controls were used to render the recording and interpretation of the observations as valid and objective as possible. A placebo (calcium lactate) was used in conjunction with cyclizine, so that direct comparisons might be made between the effects of the latter and those of what is generally accepted to be a pharmacologically inert substance. "Group" control was used during the first two weeks of the trial; 15 patients having been assigned at random to a cyclizine treatment group, and 15 patients to a placebo group. "Self" control was substituted for the former "group" control during the second two weeks of the trial, when each patient was changed over to the opposite treatment or preparation to that which he had been receiving during the first two weeks. By this method the response of a cyclizine group might be compared with that of a placebo group for the first two weeks of the trial. Furthermore direct comparisons might be made between the individual responses to each of the preparations, cyclizine and placebo, for all 30 patients included in the trial.

The tablets of cyclizine and placebo were identical in appearance, and were to be administered to the patients on a "blind" basis throughout the trial. The random assignment of patients to the two "treatment" groups, cyclizine and placebo, for the first 2 weeks of the trial, was effected in the following manner: The dispenser was given a code which consisted simply of the numbers 1–30 allocated at random to two groups A (cyclizine) and B (placebo), each group being represented by 15 numbers. The names of the 30 trial patients were sent to the hospital records clerk, with the request that he arbitrarily pair with each name a number between 1 and 30 inclusive, using each number once only. He was further requested to dispatch the paired names and numbers to the dispenser in a sealed envelope. In this way the preparation which a particular patient received during the first two weeks of the trial was determined by whether the number paired with his name, by the clerk, corresponded with Group A or Group B of the dispenser's Code. For the second two weeks of the trial each patient received the opposite preparation to that which he had already received during the first two weeks.

This system ensured, from the outset, that the cyclizine and placebo groups would be equally represented by 15 patients each; that the two groups would be unselected or unbiased in terms of the total test sample of 30 patients; that the composition of the 2 groups would be unknown to the investigators until the final decoding at the end of the trial; that each patient would receive consecutively the two preparations, cyclizine and placebo, or vice versa; and that the dispenser alone would know, at any time during the trial, which of the two preparations any particular patient was receiving.

In order that any observed changes or therapeutic effects might reasonably be ascribed to the two preparations, no other form of treatment, physical or medicinal, was administered to the patients during the trial; and the environment was stabilized in so far as that was possible.

The statistical techniques, by which any valid judgments might be made

concerning the "significance" of any observed differences in treatment effects between cyclizine and placebo, were decided upon in advance and with reference to the basic observations for recording change in the patients, which have already been described. The techniques were to be of two types, namely, a "t" test to be applied to the rating scale scores; and a simple Chi-square test to be applied, independently, to the global assessments and behaviour incidents.

The intention was to obtain an initial "score" on the rating scale for each patient at the commencement of the trial, and a subsequent score at the end of two weeks. From these scores the individual "improvement" scores for each patient were to be determined. The Mean Improvement Scores for the cyclizine and placebo groups might then readily be calculated; and the "significance" of any difference between these two means might be computed by a "t" test. If the mean initial scores for the cyclizine and placebo groups showed a marked disparity, one assumes that it would have been necessary to carry out a covariance analysis to "adjust" for this discrepancy. However, as can be seen in Table I, the mean initial scores for the two groups proved to be identical,

TABLE I

*Rating Scale Scores for First Two Weeks of Trial Using Group Control*

| | Placebo Group (15 patients) | | | | Cyclizine Group (15 patients) | | |
|---|---|---|---|---|---|---|---|
| | Initial Score | Final Score | Improvement Score | | Initial Score | Final Score | Improvement Score |
| Total .. | 464 | 428 | 36 | Total .. | 464 | 444 | 20 |
| Mean .. | 30·9 | 28·5 | 2·4 | Mean .. | 30·9 | 29·6 | 1·3 |

t=0·48, df. 28, P> ·05; (t value of 2·05 required for significance at 5 per cent. level of confidence).

30·9 for both. (A testimony to the capacity for randomization to achieve a remarkable degree of parity.) As a result of this, no such "adjustment" was necessary to the initial scores, and a "t" test could validly be applied to test the significance of any difference in the subsequent Mean Improvement Scores for the two groups. With regard to such factors as diagnostic types, severity of illness, age, and duration of illness, etc., the two groups were equally comparable. For example, all the patients were males, and all were chronic disturbed schizophrenics; the average duration of illness was found to be identical for the two groups, being 21·3 and 21·3 years.

Global or clinical assessments were to be made on each patient at the end of 2 weeks, and again at the end of 4 weeks, by which time all 30 patients would have received both preparations. A total of 60 such assessments would then be available for analysis with 30 of them coinciding with the administration of cyclizine, and 30 with placebo. These two sets of 30 clinical assessments might then be directly compared, and the "significance" of any difference between them determined by a Chi-square test. (In the final event 2 sets of 29 such assessments were available for comparison, as one patient was withdrawn from the trial after two weeks, as a result of anorexia.) The totals of abnormal behaviour incidents as abstracted from the appropriate charts, and identified as having been associated with cyclizine or placebo treatment respectively, were to be subjected, like the global judgments, to a Chi-square test of significance.

The trial was to be of 4 weeks duration. Each patient was to receive, either in the first or second 2-week period of the trial, 150 mg. of cyclizine

daily by mouth, followed by 300 mg. daily for a further week, in the form of tabs. 50 mg. 1 t.d.s. and tabs. 50 mg. 2 t.d.s., respectively. Likewise, each patient was to receive placebo as tabs. 1 t.d.s. for one week, followed by tabs. 2 t.d.s. for a further week; either in the first or second period of the trial. The method by which it was determined as to which of these two regimens a particular patient received first, or second, has already been described.

No specific attempt was made to investigate the toxicology or side-effects of cyclizine during this trial. The compound has been on the market long enough now for it to be considered comparatively safe and non-toxic; and moreover any conclusions concerning its toxicity based upon such a short trial as this, would be both presumptuous and insignificant against the background of what is already known about the compound in this respect.

## Results

The results of all the observations made during the course of the trial are presented in summary form in Tables I to III. Underneath each Table the result

Table II

*Global Assessments for Whole Trial, with Each Patient Acting as His Own Control*

| Response | Cyclizine Periods | Placebo Periods | Total |
|---|---|---|---|
| Improvement .. .. .. | 8 | 12 | 20 |
| No change .. .. .. | 19 | 14 | 33 |
| Worse .. .. .. .. | 2 | 3 | 5 |
| Total .. .. .. | 29 | 29 | 58 |

Combining categories "worse" and "no change": $\chi^2 = 0 \cdot 68$, df. = 1, $P = \cdot 4$; (Chi square value of 3·84 required for significance at 5 per cent. level of confidence).

Table III

*Abnormal Behaviour Incidents Recorded During Trial*

| | Noisy Outbursts | Aggressive Acts | Incontinence | Insomnia |
|---|---|---|---|---|
| Cyclizine .. .. | 143 | 5 | 21 | 11 |
| Placebo .. .. | 134 | 9 | 28 | 11 |
| Total .. .. | 277 | 14 | 49 | 22 |
| Differences .. .. | P> ·05 | P> ·05 | P> ·05 | — |

of the appropriate statistical analysis is stated in the conventional manner. The analyses are, in each instance, based upon the null hypothesis which is a necessary and fundamental pre-requisite. In the present analyses the null hypothesis states that "there is no difference in the treatment effects between cyclizine and placebo and any observed differences, therefore, are attributable to chance". The P values then indicate in what percentage of a number of repetitions of the trial, differences as large as those observed to obtain between cyclizine and placebo, would be expected to occur on the basis of "chance". A P value of ·05, or less, indicating that such differences would be expected to occur by chance in only 5, or less than 5, out of a total of 100 repetitions of the experiment, is generally accepted by convention as justifiable grounds for rejecting the null hypothesis. Rejection at the 5 per cent. level of confidence, as it is termed, would imply that the observed differences between cyclizine

and placebo probably reflected real differences in treatment effects. It would not, and indeed by its very nature could not, rule out absolutely, however highly significant the P value, the possibility that chance was the operative factor. None of the P values, as may be seen recorded, reached anything approaching the 5 per cent. level of confidence, and so there are insufficient statistical grounds for rejecting the null hypothesis. The conclusion necessarily follows that the trial results failed to differentiate between the treatment effects of cyclizine and placebo.

## Discussion

In reflecting upon the trial as a whole certain salient points emerge. Their importance may warrant individual consideration in some detail.

The "blindness" of the trial which is of such paramount relevance to the objective validity of the results, was effectively preserved throughout. A variety of factors may have contributed to the success of this aspect of the investigation, including some, if not all, of the following: (*i*) Scrupulous randomization coupled with a fixed and pre-determined design which is inexorably adhered to throughout; (*ii*) A deliberate restriction of the object of the trial to an exploration of the therapeutic, as opposed to any toxic, effects of the drug; (*iii*) The singular freedom of cyclizine from any obtrusive and identifiable side-effects; (*iv*) An objective and scientific orientation to the trial as an experiment, rather than any disproportionate interest or pre-occupation with the test preparations themselves; (*v*) The comparatively short duration of the trial; for given enough time, however slight the side-effects of the test compound, "the penny will drop" and it is for this reason that the "blindness" must be suspect of those trials in which a particular preparation is administered to the same patients for a period extending over many months.

The three main, and different, types of observations, recorded in the course of the trial, contributed consistently to the same answer; namely, that cyclizine was not more therapeutically efficacious than the placebo. Such an observed consistency, between different data, provides a more reliable and convincing answer than deductions based upon one set of clinical observations. Objective and verifiable facts, such as behaviour incidents, provide a valuable check on the more subjective impressions of the clinician. The greater the number and variety of relevant clinical observations, recorded during a trial, the more reliable and comprehensive may be the final assessment of the test drug.

The imperative need for placebo control, when attempting to assess a new drug, has been pre-eminently illustrated. Cyclizine was associated with a 28 per cent. recorded improvement rate, in terms of conventional clinical judgments. This might all too readily have given rise to excessive enthusiasm, and false specific claims, were it not that the 41 per cent. improvement rate associated with the placebo afforded a proper perspective for viewing the therapeutic performance of cyclizine.

The recorded clinical observations must be subjected to some form of statistical analysis before any reliable deductions can be made from them. Simply "looking at" the two improvement rates of 27·6 per cent. and 41·4 per cent. for cyclizine and placebo respectively, might give one the impression that there is a noteworthy or significant difference between them. The application of a simple statistical test to the difference between these two proportions may help to dispel such an illusion. (Difference in proportions=13·8, Standard Error=12·35, Difference not statistically significant.) It is frequently and derisively suggested that "statistics can be made to prove anything". This,

however, is a travesty of the truth. Statistics can never provide proof of a cause and effect relationship, and no reasonable statistician, one imagines, would ever claim that they could. They may, nevertheless, enable one to formulate a precise statement as to how often the observed results of an experiment might be expected to occur again upon the basis of chance alone in a specified number of repetitions of that experiment. In fulfilling this function of determining the "probability" of observed phenomena, statistical method and analysis become the arch-enemy of wishful thinking.

The compelling need would seem to be for stringent and disciplined comparative trials of all new tranquillizers before any unsubstantiated claims, however eloquent, should be accepted. The necessary scientific discipline is exemplified by the work of Hargreaves *et al.* (1), Raymond *et al.* (2), Thorpe and Baker (3), from which we personally have derived much of our methodology, and we would like to acknowledge our debt to these authors in particular. The new biochemical approach to psychiatry, which is so full of rich potentialities, may benefit if unbridled enthusiasm is checked by the rein of critical enquiry.

SUMMARY

A "blind" controlled trial of cyclizine in the short-term treatment of chronic psychosis was carried out. The object was to determine whether cyclizine is a potential tranquillizer. Thirty chronic disturbed schizophrenics received cyclizine and a placebo alternately. The design enabled group comparisons to be made between the effects of the two preparations, and also afforded direct comparisons between the responses of each individual patient to both preparations administered consecutively. The criteria of therapeutic response were based upon rating scale scores, clinical assessments, and the recording of abnormal behaviour incidents. A simple statistical analysis failed to reveal a "significant" difference between the treatment effects of cyclizine and placebo in terms of the observations made on the 30 patients included in the trial. From this it was deduced that cyclizine is not a specific tranquillizer. However, a considerable improvement rate was recorded for both preparations, and the possible implications of this fact were emphasized in relation to the extravagant claims so frequently made for tranquillizers in general.

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