A CLINICAL TRIAL OF LARGACTIL (CHLORPROMAZINE), STEMETIL (PROCHLORPERAZINE) AND VERACTIL (METHOTRIMEPRAZINE)

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INTRODUCTION

MANY phenothiazine derivatives are now in use in the treatment of schizophrenia. We, in this hospital have used Largactil extensively and more recently Stemetil in the management of chronic schizophrenia.

The latter drug was the subject of a controlled investigation which did not involve the double-blind technique (Milne and Berliner).

Since the above series a new phenothiazine—methotrimeprazine (Veractil) has been recommended by many authorities for the control of schizophrenia.

Veractil bears resemblance to both chlorpromazine and promethazine pharmacologically.

Original clinical investigation carried out by the French suggested that only a quantitative therapeutic difference existed between the two.

According to Deschamps and Madre six out of 14 long-standing female schizophrenics who had previously failed to respond to other forms of treatment were greatly improved—and a further 5 slightly improved.

Lambert, Beaujard *et al.* found in 28 cases of chronic schizophrenia, the response was equivalent to that obtained by chlorpromazine, but disturbed behaviour was not influenced as favourably as with chlorpromazine.

Deschales, Lanteri-Lausa and Fargeon found in 22 cases suffering from chronic schizophrenia, half were slightly improved and the remainder unchanged or worse. They concluded over a larger series that methotrimeprazine was somewhat less effective than chlorpromazine.

Gurtler, Soos, and Haumonte came to the conclusion that in schizophrenia Veractil was palliative and tranquillizing with no effect on the psychotic basis, this being at variance with the effect of chlorpromazine.

In the use of Veractil the above authorities noted an increase of somnolence in their patients. There were no gross extra-pyramidal side-effects but postural hypotension appeared frequently.

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The purposes of our investigation were:

1. To compare the relative efficiency of Largactil, Stemetil and Veractil.
2. To substantiate or refute the results of the previous clinical trial of Stemetil undertaken by one of us (H.B.M.) using on this occasion the double-blind technique.

Material and Method

The patients in this trial consisted of 100 male chronic schizophrenics ranging in age from 17–61. No attempt has been made to classify these patients into a particular type of schizophrenia owing to the high average duration of stay in hospital. All the individuals selected for this trial had previously been receiving treatment with one or more phenothiazine derivatives for a considerable period. Severely subnormal and leucotomized patients were excluded from selection.

The 100 patients were divided arbitrarily into 4 groups of 25 by the chief male nurse using as criteria (1) equivalent average age and (2) equivalent duration of stay in hospital (in years).

The following table gives details of the composition of the groups and previous treatments.

Table I

Group	Average Age in Years	Average Duration of Stay in Hospital in Years	Age Span	E.C.T.	Insulin	Largactil	Stemetil
1 ..	38	13	27–61	17	3	25	13
2 ..	43	13	17–57	18	6	25	11
3 ..	46	15	25–58	16	7	25	9
4 ..	42	12	27–60	17	8	25	15

It was decided to use the following dosage scheme at the commencement of the trial:

(*a*) Largactil .. .. 75 mg. t.i.d.
(*b*) Stemetil .. .. 25 mg. t.i.d.
(*c*) Veractil .. .. 50 mg. t.i.d.

the dosage of each was selected on the basis of previous and reported clinical experience.

Identical tablets were used.

The pharmacist made the initial allocation of individual active drug and inert tablet to each group in particular.

It was further decided, at the commencement of the trial that if a particular group obviously showed persistent signs of deterioration due to being on a placebo, the pharmacist would (1) add an active drug to this group, (2) by further manipulation add an inert tablet to leave the active dosage of Stemetil intact, and (3) double the dosage of the Largactil and Veractil groups.

Prior to the commencement of the trial, which was of 24-weeks duration, each group was allowed to settle in their new and uniform environment. During this period routine blood chemistry, urine analysis, basal blood pressure, body temperature and weight were noted. During the trial pulse and temperature were recorded diurnally and blood pressure daily, for the first week and

thereafter every 3rd week until the end of the trial. The blood chemistry—including liver function tests—was repeated at similar intervals. The weight was recorded weekly.

The nursing staff were requested to note any specific side-effects. Patients were allowed parole again when the initial period of deterioration was reversed and were encouraged to take part in occupational therapy and other social activities.

Behaviour was assessed by the nursing staff using a behaviour rating scale described by Baker and Thorpe and used by one of us in a previous trial (Milne and Berliner).

This commenced while each group was on routine treatment.

The nursing staff marked each patient's behaviour daily from Monday to

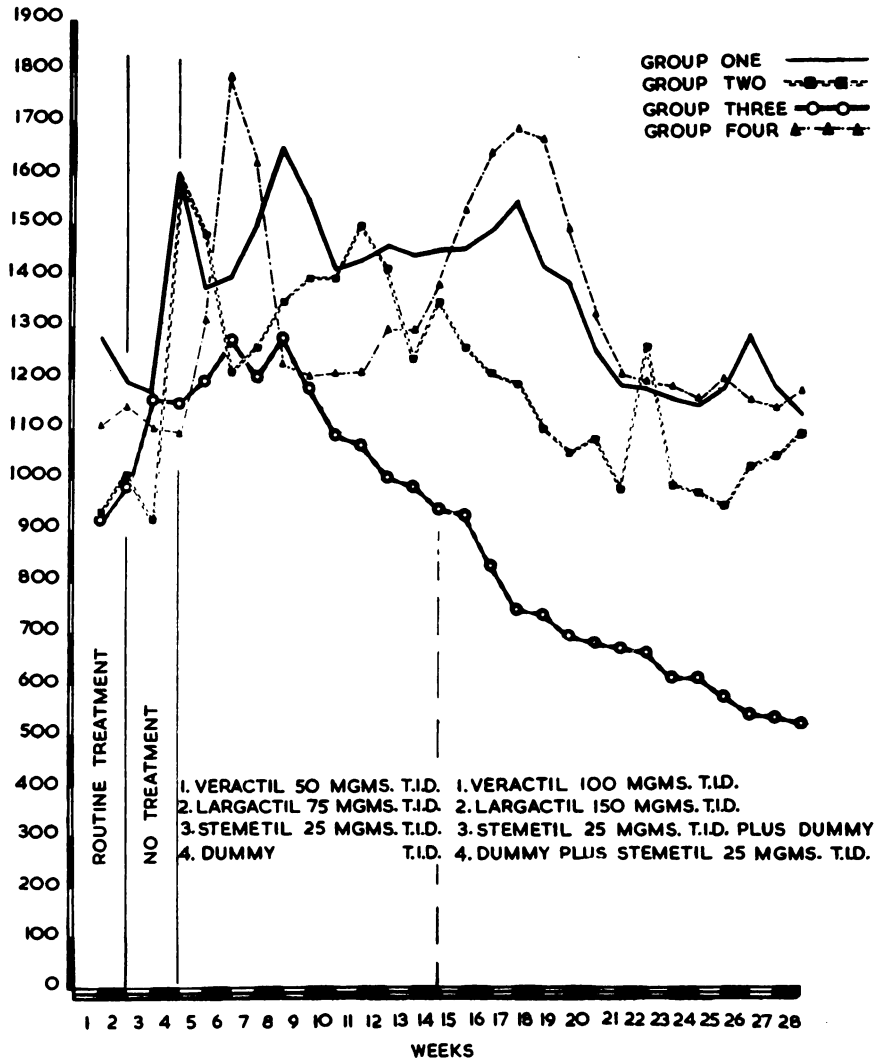

FIG. 1

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Friday. The daily scores in each group were summated weekly both for individual factors and overall behaviour.

The weekly total group scores were graphically represented as shown in Figure 1.

Individual factorial scores although not charted will be commented upon. Active routine therapy was withdrawn abruptly for a period of two weeks, which was found to be of sufficient duration to allow measurable deterioration of behaviour. It is of interest to note in this series, as in the previous trial, that within 2 weeks of withdrawal of an active preparation there was marked deterioration of behaviour of the chronic schizophrenic. This observation which has been repeatedly seen in other cases not included in this trial is in direct contradiction to the evidence presented by Good, MacSterling and Wayne Holtzman who state that chlorpromazine can be withdrawn from chronic schizophrenic patients for at least 10–12 weeks without any noticeable regression in behaviour or intellectual functioning.

RESULTS

As the objects of this trial were two-fold, i.e. (1) to compare the relative efficiency of Largactil, Stemetil and Veractil and (2) to substantiate or refute the results of the previous clinical trial of Stemetil—we propose to analyse our data (*a*) by individual group and (*b*) by a comparison of groups.

(a) *Individual Groups*

Group 1. (Tabs. Veractil 50 mg. t.i.d. for 10 weeks—increased to 100 mg. t.i.d. for remainder of trial.)

There was an initial further deterioration in behaviour lasting four weeks followed by a relative improvement up to the point at which the dosage was doubled. From this date behaviour improved until at the end of the trial the total weekly behaviour was equivalent to that which obtained at the commencement. Analysis of individual factors corroborated this lack of improvement and further analysis did not substantiate an increased drowsiness reported by other authors.

Clinically it could be said that all members of this group came under the heading of no improvement.

Group 2. (Tabs. Largactil 75 mg. t.i.d. for 10 weeks—increased to 150 mg. t.i.d. for remainder of trial.)

Following initial dosage there was an immediate improvement in the first week—probably due to a placebo effect—which was followed by a deterioration lasting 5 weeks and then a steady improvement occurred following the increase of dosage to 150 mg. t.i.d.

At the end of trial the behaviour rating was approximately similar to that at the commencement.

Analysis of individual factors confirmed a lack of response.

As in Group 1 the clinical results for individual members came under the heading of "no improvement".

Group 3. (Tabs. Stemetil 25 mg. t.i.d. for 10 weeks—then combined with dummy tablet for remainder of trial.)

Following initial dosage there was some deterioration over a period of four weeks followed by a steady and progressive response to treatment up to 10 weeks at which time the rating was lower than at the commencement.

Following the introduction of dummy there was no obvious dramatic fall and in fact the rating continued to drop until the completion of the trial at which time the behaviour score was approximately half the original.

Analysis of individual factors showed this to be due to a response in Factors A, G and L (Baker and Thorpe).

Factor A—concerned with the phenomenon of somnolence.

Factor G—concerned with the property of spontaneous speech.

Factor L—concerned with the ability to make friends.

It is of interest to note that in the previous clinical trial of Stemetil, improvement was also noted in the similar constellation of factors.

Clinically it was observed that improvement in this group was largely measured by an increase in tidiness, personal hygiene and willingness to work without supervision. Patients who had been previously asocial and monosyllabic became friendly and comparatively voluble. In this group the results could be summarized as follows:

Discharged	2
Much improved	6
Improved	11
No change	6

Group 4. (Dummy tabs. t.i.d. for 10 weeks—then combined with Stemetil 25 mg. t.i.d. for remainder of trial.)

Following initial dosage there was marked deterioration lasting 1 week only. This followed by a dramatic improvement over the next three weeks which was in our opinion a placebo response. Behaviour then steadily deteriorated over the next five weeks at which juncture the pharmacist decided to intervene and introduced Stemetil 25 mg. t.i.d.

The behaviour continued to deteriorate for a further 3 weeks and then steadily improved. At completion of trial the rating was equivalent to the original but the duration of active therapy was only 14 weeks as opposed to 24 weeks. It was felt that further improvement would have taken place if the trial had been prolonged.

Analysis of individual factors confirmed this lack of response.

Clinically the results for individual members came under the heading of "no improvement".

(b) *Comparison of Groups*

The relative efficiency of our three active preparations, according to behavioural analysis, suggests that in the long-term treatment of chronic schizophrenia Stemetil is most efficient. It would appear that Largactil is of secondary importance and finally Veractil of little value.

Further it would seem that the Veractil response was equivalent to treatment with placebo. It does seem apparent that doubling the dosage of Largactil and Veractil did produce an increased efficiency.

It will be seen that there was no alteration in dosage in Group 3 and equating this dosage (25 mg. t.i.d.) against a maximum dosage of Largactil 150 mg. t.i.d. and Veractil 100 mg. t.i.d. would completely confirm the previous observations on the efficacy of Stemetil in much smaller dosages. It has been previously suggested that the active dosage of prochlorperazine is one-third of the active chlorpromazine level. It would appear therefore that this has been an underestimation.

No statistical evidence has been produced in this trial although statistical analysis of the results has been made.

The graph in itself shows the significant findings. The statistician who surveyed our results commented upon one fact. On analysis of daily factorial scores he found a regular deterioration in rating from Monday to Friday each week. We feel that this was probably due to a fatigue element in the nursing observers.

Side-Effects and Complications

This series was distinguished by the absence of side-effects. When occurring they were of minimal importance.

Group 1—there were two hypotensive attacks occurring in the 2nd and 3rd week of therapy.

Group 2—no side-effects.

Group 3—no side-effects.

Group 4—hypotensive attack while on placebo—which therefore can be discounted.

One patient developed Parkinsonism whilst receiving placebo plus Stemetil.

Analysis of blood chemistry and liver function tests showed an interesting feature. Four cases in Group 4, while on placebo, developed positive thymol flocculation, and turbidity and a positive Van den Bergh response. It can only be presumed that this was a sub-clinical infective hepatitis.

It can be emphasized that contrary to many authors there appears to be little danger of extra-pyramidal side-effects while using Stemetil at this level.

It will be seen that out of 50 patients receiving Stemetil in this series there was only one case of Parkinsonism.

Summary

A comparison of the relative efficiency of three drugs—Largactil, Stemetil and Veractil—was undertaken. It was found that of these agents Stemetil was the most efficient, followed by Largactil and Veractil in that order. We have not been able to confirm the therapeutic efficiency of Veractil in the treatment of chronic schizophrenia.

By using the double-blind technique we have confirmed our initial observations regarding the mode of action of Stemetil.

The trial was characterized by the low incidence of side-effects.

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