Butriptyline Hydrochloride and Imipramine Hydrochloride in the Treatment of Non-Psychotic Depression

A DOUBLE-BLIND TRIAL

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SUMMARY

A comparison between butriptyline hydrochloride and one of the most widely-used tricyclic antidepressants, imipramine hydrochloride, was undertaken in 28 patients suffering from non-psychotic depression in a double-blind trial. Three criteria—side-effects, depression and anxiety—were observed at each visit. The scoring system representing degree of change from one visit to the other ranged from −2 to +10, higher values indicating better reactions to the drug. For each patient, the changes in individual criteria were accumulated up to the patient's last visit. The number of patient observations per pair at weekly or fortnightly intervals varied between 2 and 5. Butriptyline hydrochloride was superior to imipramine hydrochloride in accumulated change on all three criteria, the difference being statistically significant at the 99% level ($P<0,01$).

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Butriptyline hydrochloride is a new antidepressant with pharmacological properties similar to other tricyclic antidepressant drugs, notably imipramine and amitriptyline. Chemically, butriptyline hydrochloride is dl-10, 11-dihydro -*N*, *N*, β-trimethyl-5H-dibenzo (a,d) cycloheptene-5-propylamine. Its toxic dose (TD) and its lethal dose (LD_{50}) in rats and mice are far below those of imipramine.[1]

The compound is not a mono-amine oxidase inhibitor. Its pharmacology was investigated by Herr, Stewart and Voith.[1] The drug was initially put to clinical trial in France by Gayral, who concluded that butriptyline hydrochloride was a potent antidepressant psychotropic agent, indicated in mild and intermediate forms of depression and melancholia and successful in a high percentage of cases. It was also studied by Grivois[1] who reported that butriptyline was easy to manage, and useful for fast control of anxiety and as an antidepressant for supportive outpatient psychotherapy.

Other investigators have utilised butriptyline hydrochloride for a variety of syndromes, viz. neurotic anxiety and reactive depression, anxiolysis and enuresis control in paediatrics, endogenous depression and involutional melancholia, and the post-suicide syndrome.[1] The dosage utilised by the investigators on their adult patients varied from 25 to 50 mg of butriptyline hydrochloride 3 - 4 times per day.

The accurate assessment of psychiatric trials is fraught with difficulty. The terminology used is frequently misleading and often only applicable to separate and specific schools of psychological thought. The patients themselves supply the investigator with a subjective impression which has to be objectively documented into a statistically meaningful format. If the psychiatric investigator writes down impressions such as good, worse, mild deterioration, etc., these subjective descriptive impressions pertain to his assessment of the patient on that specific day only, hence uniformity is lost. Many authors have attempted to grade various aspects and symptoms of depression in order to subclassify the different variables.

When one has the task of comparing a new psychotherapeutic drug with another which has been in use for some time, the situation becomes more complex. One may compare the experimental drug with a placebo on a double-blind basis from which one concludes that the drug results are superior to the placebo effect. This comparison serves as no guideline to the profession. It was considered that the new preparation should be accurately compared to a standard one with regard to the effect of each upon measurable components of anxiety, depression, side-effects, and the timeous occurrence in the patient, together with severity of the latter components.

PATIENTS AND METHOD

Many constants had to be standardised before the instigation of the trial:

1. The trial had to be double-blind.
2. The new therapeutic agent and the standard antidepressive drug had to be given to matched patient pairs according to their age, sex and diagnosis.
3. The distribution of both drugs had to be randomised.
4. The diagnoses of the matched pairs had to be similar according to fixed criteria.

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5. The dosage of both preparations had to be standard in each case, and variations of dosage were to progress along similar lines with both drugs.
6. The paired patients had to be seen at equally distributed intervals by the same investigator.
7. Failure of one of the methods of therapy was defined as a rapid deterioration over two weeks of trial time. Cases showing a rapid deterioration before they had completed two weeks on either drug had to be dropped from the trial, and a similarly matched patient, according to the above patient selection criteria, recommenced on the same preparation. The reason for this was to allow two weeks on either drug to elapse before any judgement of efficacy could be made.
8. Patients were to be assessed either every week or every fortnight, after the initial consultation, on between 2 and 5 occasions.

Patient Assessment

At every visit, each patient was assessed according to a rating scale specifically for side-effects, depression and anxiety. The numeric was encircled by the investigator on every occasion.

TABLE I. EXAMPLES OF RATING SCALES

Side-effect

− 2	Patient feels very bad	
− 1	Therapy has to be discontinued	
0	Side-effects just bearable	
1	Severe side-effects	Continuously
2		Of diminishing frequency
3		Only sometimes
4	Moderate side-effects	Continuously
5		Of diminishing frequency
6		Only sometimes
7	Continuous	(Routine placebo or non-drug
8	Occasional	related complaints)
9	Patient has no complaints	
10	Patient feels much better	

Anxiety and depression (from − to +10)		Patient response
− 2	Significantly	Worse
− 1	Slightly	
0		Unchanged
+ 1	Very slow onset of	Mild improvement
+ 2	Moderate onset of	
+ 3	Fast onset of	
+ 4	Gradual	Significant improvement
+ 5	Rapid	
+ 6	Slow onset of	Good results
+ 7	Rapid onset of	
+ 8	Slow onset of	Excellent results
+ 9	Rapid onset of	
+10		Complete cure

Selection of Patients

To simplify the existing multiplicity of diagnostic classifications,[2-4] depressions were considered as falling into two broad categories, psychotic and non-psychotic. In this trial, only ambulatory patients with the non-psychotic depressive syndrome were studied. Non-psychotic depressions, whether they be part of a cyclic phenomenon (such as manic depressive illness) or merely consisting of a single episode, have the following features in common:

1. A pervading feeling of melancholia. The patient may verbalise this, and appear to be listless and apathetic.
2. A variation in the intensity of the above. The patient often feels worse in the early hours of the morning, and this subjective observation eases towards early evening.
3. Marked feelings of unworthiness.
4. A preoccupation with suicide.
5. A disturbance in sleep rhythm. The depressive loses the second trough of the sleep cycle, wakes in the early hours and has difficulty falling asleep again.
6. Loss of appetite coupled with weight loss.
7. A preoccupation with hypochondriacal ideas.
8. Diminution of libido.

Only ambulant patients having the above non-psychotic depressive syndrome were admitted to this trial.

The patients in the trial were matched in terms of sex, age and diagnosis, their common denominator being the diagnosis of a non-psychotic depressive reaction with the above features already described.

Dosage

Sealed containers labelled 1a or 1b were utilised. The container held either butriptyline hydrochloride 25 mg or imipramine hydrochloride 25 mg. The same patient received the same trial index number throughout the study, and patients were involved as intimately as possible in the handling of the trial. The principle of informed consent was strictly adhered to. They knew that both containers allocated to them would contain a preparation that would lift their depression, and the patients were agreeable to acting in a double-blind trial of this nature. It was agreed to refer to the preparation merely as the medication, and not as the pill or the tablet, to preserve the anonymity of the medication. This was understood by each patient. There was considerable interest in being actively involved in a drug study and many patients seemed pleased to explore as carefully as they could how they felt on the medication. The author had no prior knowledge of the randomisation of the two therapeutic agents involved in the trial. Great pains were taken to ensure that neither of the two agents was visible through the container and that the author would have no physical contact with the containers at all.

All interviews began with a simple rating of their state of well-being and the presence of side-effects. This was done in an open discussion with the patient, and the final

TABLE II. ACCUMULATED CHANGES IN SYMPTOMS

	On butryptaline hydrochloride			On imipramine hydrochloride			
Patient No.	Side-effects	Depression	Anxiety	Patient No.	Side-effects	Depression	Anxiety
1	28	27	27	1	2	− 2	− 3
2	11	2	2	2	24	7	4
3	33	25	24	3	19	20	17
4	9	6	8	4	0	0	0
5	17	14	16	5	13	− 1	0
6	33	30	28	6	5	− 4	− 2
7	9	5	2	7	4	0	− 2
8	9	0	0	8	9	0	0
9	27	19	17	9	14	4	1
10	27	19	12	10	16	23	15
11	18	1	1	11	5	6	5
12	27	11	14	12	4	4	1
13	27	19	23	13	27	6	3
14	17	5	3	14	18	8	2
X	20,9	13,1	12,6		11,4	5,1	2,9
S	9,0	10,2	10,2		8,5	7,9	6,0

figures circled on the rating scale were seen by the patient. As soon as the form was completed, it was sealed and sent to the statistical co-ordinator of the trial. In this way, each assessment was done without the guideline of an earlier rating to set the stage or bias the results in any way. Ratings were done once a week or fortnightly.

STATISTICAL METHOD AND RESULTS

A measure of the over-all effect of treatment is provided by the accumulated change in symptoms on each of the three criteria. These scores were computed for each subject and are listed in Table I. A conspicuous feature of the data is the tendency for high scores on one of the criteria to be associated with high values on the other two.

Since the members of each pair were matched, a suitable measure of the difference in the effect of the two drugs is obtained by taking the difference in accumulated change between the two members of each pair. Table II shows these differences, the score of the imipramine hydrochloride subject having been subtracted from that of the butriptyline hydrochloride subject in each case. Most of the differences are positive, suggesting that butriptyline is superior. To test this hypothesis, the Wilcoxon matched pairs signed rank test was used. This test showed that on each criterion butriptyline hydrochloride was superior to imipramine hydrochloride, the differences being statistically significant at the 99% level ($P < 0{,}01$).

The use of Bonferroni's inequalities shows further that at a significant level of at least 97%, butriptyline hydrochloride is superior to imipramine hydrochloride on all three criteria simultaneously. In fact, of the 10 pairs in which one drug performed better than the other on all three criteria, 9 favoured butriptyline hydrochloride and one imipramine hydrochloride. This difference is statistically significant at the 99% level ($P = 0{,}01$), and yields the estimate that approximately 70% of the patients performed better on all three criteria on butriptyline hydrochloride.

TABLE III. DIFFERENCES BETWEEN ACCUMULATED CHANGES IN SYMPTOMS IN EACH MATCHED PAIR

	Butriptyline hydrochloride minus imipramine hydrochloride scores		
Patient pair	Side-effects	Depression	Anxiety
1	26	29	30
2	−13	− 5	− 2
3	14	5	7
4	9	6	8
5	4	15	16
6	28	34	30
7	5	5	4
8	0	0	0
9	13	15	16
10	11	− 4	− 3
11	13	− 5	− 4
12	23	7	13
13	0	13	20
14	− 1	− 3	+ 1
Rank sum	8	12	9,5

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