A comparative controlled clinical study of butriptyline ('Evadyne'), in standard and sustained-release formulations, in the treatment of depression

Psychopharmacological Unit and CIPUL, University of Liège, Wallonia, Belgium

J. Collard, St. Diricq and M. Ansseau

Pharmatherapeutica, (1979), **2**, 260. *Paper received:* 30th January 1979

SUMMARY

Thirty-one patients with endogenous, endoreactive or exogenous depression, usually associated with anxiety, participated in a randomized, double-blind controlled study designed to compare the therapeutic efficacy and tolerance of butriptyline (75 mg per day for 6 weeks), given either in its regular form or as a sustained-release formulation. Patients in one group received 3 daily doses of 25 mg butriptyline; those in the other group received a single 75 mg daily dose at bedtime of the sustained-release formulation plus 2 doses of placebo during the day. All patients were assessed by means of 5 psychometric scales (Hamilton, BPRS, NOSIE, Cattell and CGI) before the start of therapy, after 3 weeks and after 6 weeks. Biological parameters (blood, liver, ECG and EEG) were also controlled. The results of the psychometric assessments showed that butriptyline, in both dosage forms, was consistently effective and produced marked improvement in rating scores in the majority of the patients. The few side-effects reported were mild and transient, and were mostly of the classical anticholinergic type. The sustained-release form, given once daily, provided simplicity and convenience of administration, resulting in improved patient acceptance and improvement in sleep disturbances.

Key words: Butriptyline – sustained-release preparations – depression

INTRODUCTION

The role of medication in the treatment of various forms of depressive states is well established. At present, the principal concern of the clinician is the selection of the antidepressant agent which will best serve the needs of every individual patient. Because of our previously favourable experience with butriptyline hydrochloride ('Evadyne'†), a tricyclic antidepressant with anxiolytic properties, rapid onset of action and almost negligible toxicity,[7,8,13] we have undertaken a study of the existing formulation of butriptyline, given in 3 daily doses, in comparison with a new sustained-release form, designed for single daily dose administration. The main purpose of our investigation was the assessment of the therapeutic efficacy and tolerance of the sustained-release form in the treatment of depression.

PATIENTS AND METHODS

A total of 35 patients entered the study. All were in-patients at the 'Bavière

Paper originally presented at the 11th C.I.N.P. Congress, 9-14 July 1978, Vienna, Austria
†registered trade mark, Ayerst

University Hospital' (Liège University, Psychiatric Clinic, Psychopharmacological Unit and CIPUL). The group comprised both previously hospitalized patients and new admissions.

Depressive illness was the principal diagnostic category used for admission to the trial. Depressive neurosis (DSM II 300.40, reactive depression or depressive reactions), and psychotic depressive reactions (DSM II 298.00) were the two forms most frequently diagnosed on the basis of the following evaluations: (i) investigator's clinical judgement, i.e. research psychiatrist's diagnosis, (ii) recent psychiatric case record, i.e. ward psychiatrist's diagnosis, (iii) psychometric scores on the Hamilton Rating Scale for Depression (HAM), the Brief Psychiatric Rating Scale (BPRS), Nurses' Observation Scale for In-Patient Evaluation (NOSIE), Cattell, and the Clinical Global Impression Scale (CGI). In order to qualify for admission, patients had to score a minimum of 15 points on the Hamilton scale. Items Nos. 1, 2, 3, 4, 10, 11 and 13 were included; items Nos. 6, 17, 18, 19 and 20 were excluded from consideration. Patients were enrolled in the study only if the research psychiatrist's judgement coincided with results of the psychometric scores.

All patients received a complete physical examination at admission; this included a full assessment of haematologic parameters, liver function tests, ECG and EEG. Patients were disqualified if their initial physical examinations revealed the presence of contra-indications for the evaluation of tricyclic agents, such as allergies and/or hepatic, cardiac, haematologic, pulmonary or renal dysfunction or disease. Patients currently considered to be drug failures to antidepressant agents, and those having received electroconvulsive therapy within the last 3 months were not enrolled. Furthermore, patients were excluded if they presented with one or more of the following conditions: organic brain syndrome, history of CNS disease, history of convulsive disorder, moderate to severe mental deficiency, prior psychosurgery, drug addiction, or pregnancy.

Patients were assigned on a randomized, double-blind basis to receive treatment with butriptyline (75 mg per day) either as the regular formulation or as a sustained-release preparation ('Evadyne S/R'). Because the regular form of butriptyline was given in 3 equal doses of 25 mg each, those patients allocated to the sustained-release preparation also took 3 identical capsules per day; the morning and noontime doses were placebo and the total dose of 75 mg butriptyline was given in a single evening dose. The period of drug administration was 6 weeks, preceded by a 2-week washout period on placebo. However, patients who showed exceptionally good response continued taking butriptyline and were followed up for 2 to 4 additional weeks. All patients were assessed by means of the 5 psychometric scales, before therapy, after 3 weeks and after completion of the trial (6-weeks' treatment).

During the trial period no concomitant medications were permitted except in an emergency, when a short-acting hypnotic, i.e. amylobarbitone sodium, was allowed. No form of psychological therapy, such as group or individual psychotherapy, or behaviour modification was offered. Medication for physical complaints not caused by emotional disturbances was administered only if needed.

A special form was kept, in each case, for recording the side-effects of the medication under study.

RESULTS AND DISCUSSION

Thirty-one fully completed case reports were reviewed. These related to 18 women and 13 men, ranging in age from 18 to 65 years. The patients' socio-economic background was fairly homogeneous. During the course of the trial, all were in the same treatment unit and followed essentially the same daily routine. When the trial code was broken it was found that 17 patients had received the sustained-release formulation (Group A) and 14 had received the regular formulation (Group B). Both groups were comparable with regard to patient characteristics.

As mentioned earlier, five rating scales were utilized for psychiatric assessment: Hamilton, BPRS, NOSIE, Cattell and CGI. Among these, the Hamilton scale and CGI are the more meaningful tools for the purpose of diagnosing neurotic depression. Data obtained by means of NOSIE, BPRS and Cattell are available on request but it should be noted that these rating scales are not always appropriate for the evaluation of simple neurotic depression. Moreover, some depend, to a very large degree, on the ability and the instructions given to the patient (self-rating scales) or the training of nurses (NOSIE), and BPRS is better suited for the evaluation of schizophrenia or other psychoses than for the patient material enrolled in this trial. While patients showed some definite signs of improvement on all scales, we nevertheless consider the above three (NOSIE, BPRS and Cattell) as supplementary evidence.

For simplicity and convenience in summarizing the results of this study, raw data on mean rating scores before and after treatment have not been included in this paper. Details, however, are once again available on request.

Hamilton rating assessment

Group A. Out of 17 patients receiving the sustained-release formulation of butriptyline (75 mg at bedtime), 10 showed between 80% to 94% improvement in rating scores from baseline values. This is an above average or excellent improvement, corresponding to a marked improvement on CGI scores. Five patients showed a 76% to 80% improvement, which is good or moderate improvement, and only 2 patients showed between 24% to 32% improvement, which can be considered minimal. There was no worsening of scores in patients or any non-responsive cases (Table 1).

Table 1. Summary of changes in Hamilton Rating Scale for depression scores after treatment with butriptyline in two dosage forms

Treatment	No. patients	% score improvement	Assessment of response
Group A (75 mg butriptyline sustained release capsule once daily)	10	80% to 94%	Excellent
	5	76% to 80%	Good
	2	24% to 32%	Minimal
Group B (25 mg butriptyline 3-times daily)	8	80% to 100%	Excellent
	5	58% to 72%	Good
	1	40%	Minimal

Group B Out of 14 patients receiving 25 mg butriptyline 3-times daily, 8 showed between 80% to 100% improvement in scores, which is excellent or marked

improvement. Five patients showed 58% to 72% improvement, which can be considered a moderate degree of improvement, and only 1 patient showed 40% improvement, which is minimal. In this group, Patient Nos. 14, 17 and 32 were scored as inadequate because CGI was not performed at the end of the study.

The overall percentage improvement in Group A was 77% and that in Group B was 83%. In other words, both groups responded well to treatment with butriptyline. However, we view the improvement in the patients on the sustained-release formulation to be more meaningful in that 10 out of the 17, i.e. almost 59%, showed an excellent response: this is a slightly higher proportion than seen in patients who received butriptyline in 3 equal daily doses.

CGI score assessment

Group A. Seven of 17 patients showed marked improvement, 7 showed moderate improvement, and 2 showed minimal improvement. One patient (No. 29) was not scored (Table 2).

Group B. Three of 14 patients showed marked improvement, while 7 patients presented with moderate improvement. Minimal improvement was noted in 1 patient. Three patients were not scored (Table 2).

Table 2. Summary of changes in CGI scores after treatment with butriptyline in two dosage forms

Treatment	No. patients	Clinical response assessment
Group A (75 mg butriptyline sustained release capsule once daily)	7	Marked improvement
	7	Moderate improvement
	2	Minimal improvement
	1	Not scored
Group B (25 mg butriptyline 3-times daily)	3	Marked improvement
	7	Moderate improvement
	1	Minimal improvement
	3	Not scored

As with the results of the Hamilton rating scale, patients rated on the CGI responded well to both dosage forms of butriptyline. Those on the sustained-release formulation presented the more clinically significant response but, because patient numbers concerned were small and both groups received the same active drug, statistically significant superiority of one formulation over the other could not be expected. It is reasonable to assume from the results, however, that a single 75 mg dose of butriptyline in a sustained-release formulation was equally as effective as 3 daily doses, each of 25 mg butriptyline.

Side-effects

Few side-effects of treatment were reported, and were mild in nature, being mostly of the classical anticholinergic type, such as drowsiness, dry mouth or blurred vision. They did not persist, but tended to diminish during the course of treatment.

CONCLUSIONS

Butriptyline hydrochloride is a tricyclic antidepressant which differs in many

respects from other analogues,[8] e.g. it is a potent blocker of dopamine uptake and a good central anticholinergic. Its pharmacology has been well reported,[7,8,13] and animal studies have shown its lack of interference with REM sleep. A number of investigators have reported[1-6,9-12,14] on its clinical effectiveness in patients with neurotic and reactive depression, and it has been noted to act within 7 to 14 days, to have marked anxiolytic effects and good tolerance, side-effects usually being confined to mild and transitory anticholinergic effects.

The sustained-release formulation of butriptyline ('Evadyne S/R'), given once a day at bedtime, provides further therapeutic advantages, not least of which is the convenience of administration of a single dose compared with a 3-times daily regimen. Moreover, the single daily dose, given at bedtime, is able, in most instances, to treat the sleep disturbances associated with depression, such as difficulty in falling asleep or early morning wakefulness. In our study, the use of the sustained-release preparation appeared to minimize the awareness of side-effects, treating, as it were, depression during sleep. It should afford equally effective treatment with better control of drug intake, especially in out-patients, and result, therefore, in improved patient compliance which is so often a problem in such patients.

REFERENCES

1. Alves Garcia, J., (1971). Clinical trials with butriptyline. *J. Med.*, **2**, 290.
2. Elis, B., (1971). The treatment of the post-suicide syndrome with butriptyline. *J. Med.*, **2**, 331.
3. Fiume, S., (1971). Investigation of a new antidepressant, butriptyline. *J. Med.*, **2**, 305.
4. Gonzales, M., and Montano, H., (1971). Clinical experience with butriptyline (AY-62014) in the treatment of depression. *J. Med.*, **2**, 296.
5. Grattarola, F. R., Morgando, E., and Ravarino, G., (1971). Preliminary clinical results in the treatment of psychoneurotic depression with butriptyline. *J. Med.*, **2**, 327.
6. Grivois, H., (1971). Butriptyline, a new antidepressant compound. *J. Med.*, **2**, 276.
7. Herr, F., Voith, K., and Jaramillo, J., (1971). The pharmacology of butriptyline. *J. Med.*, **2**, 258.
8. Jaramillo, J., and Greenberg, R., (1975). Comparative pharmacological studies on butriptyline and some related standard tricyclic antidepressants. *Can. J. Physiol. Pharmacol.*, **2**, 104.
9. Levinson, B., (1974). Butriptyline hydrochloride and imipramine hydrochloride in the treatment of non-psychotic depression. *S. Afr. Med. J.*, **48**, 873.
10. Madalena, J. C., and de Matos, H. G., (1971). Preliminary clinical observations with butriptyline. *J. Med.*, **2**, 322.
11. Perez de Francisco, C., Nieto Gomez, D., Castilla, J., Torres, A., and Avalos, C., (1971). Trial with a new anxiolytic antidepressant, butriptyline hydrochloride (AY-62014) Evadyne. *J. Med.*, **2**, 316.
12. Ribustini, G., and Naim, U., (1971). Clinical trials with a new antidepressant. *J. Med.*, **2**, 311.
13. Voith, K., and Herr, F., (1969). Psychopharmacological evaluation of a new antidepressant – butriptyline. *Arch. Int. Pharmacodyn. Thér.*, **182**, 318.
14. Yatco, D. D., Venzon, L., and Villadolid, L. S., (1971). Report on butriptyline hydrochloride (Evadyne) in ambulatory patients. *J. Med.*, **2**, 300.

Clinical evaluation of the symptomatic activity of a new, original psychotropic drug, minaprine

A. Garcia Maffla and M. H. de Garcia

Department of Psychology and Psychodynamics, Javeriana University, Bogota, Columbia

Pharmatherapeutica, (1979), **2**, 265. *Paper received:* 15th April 1979

SUMMARY

The symptomatic activity of minaprine, a new, original psychotropic drug, was studied in a group of 40 out-patients presenting with mild or moderate psychopathological disorders and psychosomatic symptoms, mainly related to sexual function. Patients were treated with 75 mg daily for 30 days and all other psychotropic chemotherapy was excluded during the study. Assessment of the changes in the severity rating scores of the main presenting symptoms showed that the drug acted very favourably on asthenia (including psychic), lowered daytime alertness, sleep disturbances, and psychosomatic symptoms, with excellent or good results in 60% to 90% of the cases. Anxiety, depression, irritability and aggressiveness were favourably influenced in 56% to 62% of the cases. Excellent or good overall results were obtained in 69.5% of the patients. Therapeutic benefits persisted for 1 month after stopping minaprine therapy in most of the cases. The clinical tolerance of minaprine was excellent: only 2 patients showed a slight and temporary increase in tension, which disappeared spontaneously after a few days without stopping or modifying the treatment. The results of this clinical evaluation suggest that minaprine may be a useful drug for the treatment of moderate or mild anxiety-depressive states, especially when there is a psychasthenic background, and is also effective in relieving psychosomatic (mainly sexual) symptoms. It is also suggested that minaprine should be studied in other groups of patients with psychological disorders, such as the elderly and children.

Key words: Minaprine – psychotropic drugs – psychophysiologic disorders

INTRODUCTION

Minaprine† is a new, original molecule, morpholino (2-ethylamine)-3 methyl-4 phenyl-6 pyridazine, which attracted our attention as early as 1976 because of the originality of its pharmacological profile.[1,9,15] It is difficult, in fact, to define the pharmacological class into which minaprine should be placed, because the activity of this compound is probably not due to a single mechanism of action. The biochemical effects of minaprine hydrochloride include: diminution of dopamine turnover in the brain, an increase in intra-cerebral serotonin and, possibly, an antagonistic action against glycine, which is itself an inhibitory type of neuromediator.

Although, in this respect, minaprine differs from all the major compounds used at the present time, preliminary clinical results have demonstrated that it could be qualified as having 'disinhibiting psychoanaleptic' activity.[2,13] This therapeutic profile was then evaluated clinically in a wide range of psychopathological conditions,

†*30038 CB, Clin Midy Laboratories*