Clinical Evaluation of the Antidepressants Maprotiline and Amitriptyline

A DOUBLE-BLIND CONTROLLED TRIAL

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SUMMARY

Twenty-five patients suffering from endogenous depression entered this 28-day double-blind trial to compare the efficacy and tolerability of maprotiline (Ludiomil) and amitriptyline.

Response to the two treatments was assessed by means of the Hamilton Rating Scale for Depression, and by global assessments by investigator and patient at the end of the treatment. A linear decrease in the mean total Hamilton scores over the treatment period was observed for both treatment groups.

Onset of action was noted to be more rapid in the maprotiline group. Tolerability and side-effects were evaluated by a check list of treatment-emergent signs and symptoms and a global assessment. Both treatments were equally well tolerated.

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Depressive disorders have been encountered on a steadily increasing scale during the past two decades in most industrialised countries.[1] This has brought about an intensification of research into the treatment of depression. One of the many products emerging from this research effort is Ludiomil (maprotiline). Maprotiline is only remotely related to the conventional tricyclic antidepressants. It is a tetracyclic compound with a formula $C_{20}H_{23}N$ HCl named 1-(3-methylaminopropyl)-dibenzo [b,e,]-bicyclo-[2,2,2]-octadiene hydrochloride.

Pharmacologically, maprotiline was found to inhibit the uptake of noradrenaline in several organs of different animal species. It was also found to potentiate the peripheral effects of noradrenaline *in vivo* and *in vitro;* the contractile effect of various neurotransmitters *in vitro* is antagonised.[2]

Preliminary data from an open trial in 534 depressed patients indicated that maprotiline might have some advantages over the usual tricyclic drugs; this suggested that maprotiline may have a faster onset of action, better tolerability and greater efficacy.[1]

In an attempt to evaluate these initial impressions this double-blind trial was performed. Amitriptyline film-coated tablets were chosen as the reference compound. These tablets conform to the standards quoted in the *British Pharmacopoeia* 1973. Thus the availability of active substance was ensured.

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PATIENTS AND METHODS

Patients

Inclusions. Twenty-five male and female White patients suffering from endogenous depression, who would normally be treated with tricyclic antidepressants and/or ECT, were admitted to the trial. Background information about them is given in Table I. Before the treatment the two patient groups were homogeneous.

TABLE I. BACKGROUND INFORMATION ON THE 25 PATIENTS PARTICIPATING IN THE STUDY

Characteristic	Maprotiline	Amitriptyline	Both treatments
Ages (years)			
31 - 40	1	1	2
41 - 50	4	3	7
51 - 60	6	5	11
61 - 70	2	3	5
Sex			
Male	3	3	6
Female	10	9	19
Mental illness in family			
Depression	3	7	10
Alcoholism	1	0	1
Schizophrenia	1	0	1
Other	1	1	2
Population type			
Outpatient	4	4	8
Institutionalised	9	8	17
Course of disease during previous 2 weeks			
Deteriorated	11	9	20

Exclusions. Patients who had received antidepressant therapy within two weeks before entry into the trial, pregnant women, and patients suffering from epilepsy, glaucoma, prostatic hypertrophy and severe hepatic or renal impairment, were excluded.

Method

The design of the trial was double-blind with random allocation of patients to the two treatments. The duration of treatment was 28 days, during which both trial medications were given orally in identical daily doses of 50 mg *t.d.s.* The amitriptyline used conformed to the standards reported in the *British Pharmacopoeia* 1968. The patients were submitted to a psychiatric examination before the start of medication (day 0) and subsequently on days 3, 7, 14 and 28 of treatment. The results of these assessments were recorded on the Hamilton Rating Scale for Depression.[3] Blood pressure, pulse rate, and weight were recorded at each interview. Urinalysis, full blood count alkaline phosphatase, SGOT and glucose tolerance tests were carried out on day 0 and on day 28. The onset of drug effect, as well as an opinion of over-all therapeutic effect and tolerability, were recorded. In addition, the patient's opinion of therapeutic effect was solicited. Tolerability was assessed by means of a check list of 29 treatment emergent symptoms and signs and a global assessment.

RESULTS

Efficacy

The total scores on the Hamilton Rating Scale for each patient who completed the 28-day treatment period, were submitted to covariance analysis, the pre-treatment score being used as the covariant. Although no significant difference was apparent at any time between the two subsamples, both treatments significantly decreased the mean total score over the trial period. There were too few patients in each group to obtain significant statistical differences for individual items on the Hamilton Rating Scale. However, of the 23 parameters assessed at the four treatment periods (92 in all), maprotiline was favoured 43 times, amitriptyline 34 times, and in 15 no difference was detected.

Investigator and patient assessments of the global therapeutic effect showed no significant difference between the two treatment subsamples (Tables II and III). However, if these results are considered clinically, maprotiline clearly tends to be favoured.

TABLE II. INVESTIGATOR'S JUDGEMENT OF THERAPEUTIC EFFECT

Degree of improvement	Maprotiline		Amitriptyline		Both treatments	
	No.	%	No.	%	No.	%
Marked	4	33	3	25	7	29
Moderate	8	67	7	58	15	63
Minimal	0	0	2	17	2	8
Total	12*	100	12	100	24	100

* One case not reported.

TABLE III. PATIENT'S OPINION OF THERAPEUTIC EFFECT

Degree of improvement	Maprotiline		Amitriptyline		Both treatments	
	No	%	No	%	No	%
Marked	5	42	5	42	10	42
Moderate	6	50	5	42	11	46
Minimal	1	8	2	16	3	12
Total	12*	100	12	100	24	100

* One case not reported.

Maprotiline was found to have a faster onset of action than amitriptyline, although, because of the limited number of patients in this trial, this was not statistically verified. The largest difference in response in favour of maprotiline was observed cumulatively by day 5 (Table IV).

TABLE IV. ONSET OF DRUG EFFECT (CUMULATIVE FREQUENCY RECORD)

Day of treatment	Maprotiline		Amitriptyline		Both treatments	
	No.	%	No.	%	No.	%
1	—	—	—	—	—	—
2	—	—	1	8,33	1	4,17
3	4	33,33	2	16,67	6	25,00
4	5	41,67	4	33,33	9	37,50
5	7	58,33	4	33,33	11	45,83
6	7	58,33	4	33,33	11	45,83
7	7	58,33	5	41,67	12	50,00
8	7	58,33	6	50,00	13	54,17
9	9	75,00	10	83,33	19	79,17
10	10	83,33	10	83,33	20	83,33
11	11	91,67	10	83,33	21	87,50
12	11	91,67	10	83,33	21	87,50
13	11	91,67	11	91,67	22	91,67
14	11	91,67	11	91,67	22	91,67
15	11	91,67	11	91,67	22	91,67
16	11	91,67	12	100,00	23	95,83
17 - 22	11	91,67	—	—	23	95,83
23	12*	100,00	—	—	24	100,00

* One case not reported in the maprotiline subsample.

Tolerability

Of the 18 treatment-emergent signs and symptoms reported there were 7 (39%) which showed a higher incidence in the maprotiline subsample. In the amitriptyline subsample, 11 (61%) of the 18 signs and symptoms showed a higher incidence. In the global assessment of tolerability no significant difference between the subsamples was found (Table V).

Two patients, one from each treatment subsample, failed to complete the trial, one having had a grand mal attack after 9 days of treatment on maprotiline. This patient had no previous history of epilepsy. Unfortunately

TABLE V. GLOBAL ASSESSMENT OF TOLERABILITY

	Maprotiline		Amitriptyline		Both treatments	
Side-effect	No.	%	No.	%	No.	%
No side-effect	3	25	5	42	8	33
No remarkable interference	7	58	6	50	13	54
Significant interference	2	17	1	8	3	13
Therapeutic effect nullified	—	0	—	0	—	0
Total	12*	100	12	100	24	100

* One case not reported.

no follow-up was possible. The other patient developed mental clouding attributed to diabetes after 21 days' treatment while on amitriptyline.

CONCLUSION

The small number of cases in the two treatment groups makes it difficult to draw definite statistical conclusions on the difference between the trial medications. Both treatments proved to be effective antidepressants, as evidenced by the decrease in the total scores on the Hamilton Rating Scale.

Maprotiline was marginally superior in its effect on the individual items of the Hamilton Rating Scale. The onset of drug action was faster with maprotiline. Both medications were equally well tolerated and produced no abnormal laboratory findings.

I wish to thank the Laboratory for Chemical Pathology of the University of Pretoria, for the biochemical work; and Ciba-Geigy (Pty) Ltd, for their assistance.

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