Maprotiline and Amitriptyline in the Treatment of Depressive Illness

A DOUBLE-BLIND COMPARISON

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SUMMARY

Patients suffering from depressive illness were admitted to a double-blind trial comparing the efficacy and tolerability of maprotiline and amitriptyline.

Therapeutic efficacy was evaluated by means of the Hamilton Rating Scale for Depression (day 0, 3, 7, 14, 21, 28) and by the over-all assessments of investigator and patient at the end of the treatment. Tolerability and side-effects were evaluated by an over-all assessment and by a checklist of treatment signs and symptoms.

Maprotiline was found to be markedly faster in its effect than amitriptyline. The effect of maprotiline was apparent in the majority of cases by the 4th day of treatment. The over-all improvement of patients on maprotiline was better than it was in those treated with amitriptyline, although this did not quite reach statistical significance. Tolerability was generally similar although it tended to favour maprotiline.

S. Afr. Med. J., **48**, 47 (1974).

Ever since the discovery of the effects of imipramine by Kuhn in 1957[1] the search for antidepressant medication has produced a host of other tricyclic compounds and monoamine oxidase inhibitors.

One such new product is maprotiline (Ludiomil), which was synthesised in the Research Departments of Ciba-Geigy Basel, in 1967. It is a tetracyclic compound with a formula $C_{20}H_{24}ClN$ named 1-(3-methylaminoproply)-dibenzo b, e-bicyclo-2, 2, 2-octadiene hydrochloride. The structure is shown in Fig. 1. Preliminary open trials indicated that maprotiline was therapeutically effective and well tolerated. These initial results were confirmed by controlled double-blind studies carried out by Welner[2] and Pinto *et al.*,[3] and prompted this trial which was designed to compare the efficacy and tolerability of maprotiline and amitriptyline in the treatment of depressive illness.

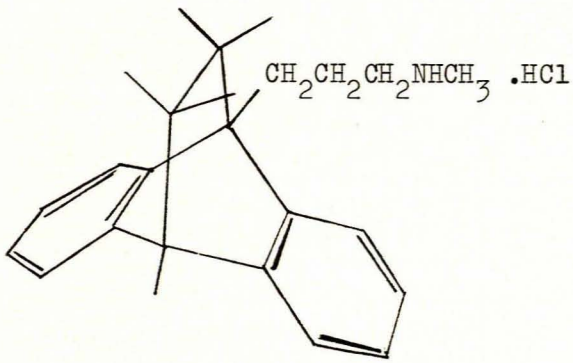

Fig. 1. Structural formula of maprotiline.

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PATIENTS

Patients with depressive illness who would normally be considered suitable for treatment with amitriptyline, were included in this trial. Ninety-three per cent of these patients presented with predominantly endogenous depression, with 59% of them showing marked agitation (Table I).

TABLE I. DIAGNOSTIC CATEGORIES AND TYPES IN THE TWO TREATMENT SUBSAMPLES

Category		Maprotiline No.	Maprotiline %	Amitriptyline No.	Amitriptyline %	Both treatments No.	Both treatments %
Predominantly endogenous	Agitated	14	64	12	54	26	59
	Retarded	4	18	5	23	9	20
	Other	3	14	3	14	6	14
Predominantly reactive	Agitated	1	4	2	9	3	7
	Total	22	100	22	100	44	100

Of the 13% of patients diagnosed as predominantly 'endogenous—other', 4 patients were classified as showing marked hypochondriacal features, and 2 patients associated psychosomatic features. Only 6,8% of the trial population were diagnosed as predominantly reactive depressive.

It is obvious from an inspection of Table I that both treatment subsamples are homogeneous with respect to diagnostic criteria of depression.

Exclusions

Patients being currently treated with monoamine oxidase inhibitors, or for 2 weeks before entry into the trial,

cases of pregnancy, epilepsy, glaucoma, prostatic hypertrophy, and severe hepatic or renal impairment, were excluded.

METHOD

The trial design was a double-blind, comparative, between-patient study, with random allocation to either of the treatments; 45 of the 48 patients who entered the trial, successfully completed the study. The trial was conducted between November 1971 and January 1973, and included 26 inpatients and 19 outpatients, distributed evenly in each treatment subsample. The products used were maprotiline 50 mg *t.d.s.*, i.e. a total of 150 mg per day, and amitriptyline 50 mg *t.d.s.*, i.e. a total of 150 mg per day. Amitriptyline was chosen because of its general acceptance as a standard antidepressant and the fact that it is widely used in South Africa. The duration of treatment was 28 days. The efficacy was assessed by means of the Hamilton Rating Scale for Depression.[4] Video tape recordings were used as an additional method of assessment for some of the cases. Evaluations were made on days 0, 3, 7, 14, 21 and 28.

In addition, unwanted effects were assessed by means of a checklist of 29 treatment-emergent signs and symptoms. Both therapeutic activity and side-effects were also generally rated at the end of the treatment.

Of the 45 patients evaluated, 23 were in the maprotiline treatment group, and 22 in the amitriptyline treatment group. The median age of the total sample was 39 years; and 58% of the patients were male. No significant difference in the sex distribution was found. The population treated was White.

With regard to family history, depression was found in 39,8% of cases, alcoholism in 10,9%, schizophrenia in 4,4%, and other psychiatric illnesses in 2,2%.

EFFICACY

Assessment of the therapeutic effects by the investigator after 28 days' treatment, showed a trend in favour of maprotiline ($P<0,1$) (Table II). Ninety-one per cent of the patients on maprotiline improved markedly or moderately, and 63,6% of those on amitriptyline, demonstrated a similar improvement. A statistically significant difference at the 0,025 level was observed in favour of maprotiline for the over-all therapeutic effect as assessed by the patients (Table III).

TABLE II. INVESTIGATOR'S JUDGEMENT OF THERAPEUTIC EFFECT

Assessment	Maprotiline		Amitriptyline		Both treatments	
Treatment effective						
	No.	%	No.	%	No.	%
Marked improvement	11	50	5	23	16	36
Moderate improvement	9	41	9	41	18	41
Minimal improvement	2	9	5	23	7	16
Treatment failed						
No change/ deterioration	0	0	3	13	3	7
Total	22	100	22	100	44	100

TABLE III. PATIENT'S OPINION OF THERAPEUTIC EFFECT

Assessment	Maprotiline		Amitriptyline		Both treatments	
Treatment effective						
	No.	%	No.	%	No.	%
Marked improvement	14	64	5	23	19	43
Moderate improvement	6	27	10	45	16	36
Minimal improvement	2	9	4	18	6	14
Treatment failed						
No change/ deterioration	0	0	3	14	3	7
Total	22	100	22	100	44	100

The total Hamilton Score from the 3rd to the 28th day of treatment decreased in both maprotiline and amitriptyline subsamples. The 2 treatment subsamples do not, however, differ significantly either during the first 3 days of treatment or at the subsequent assessments, although a trend in favour of maprotiline emerges. Analysis of the individual items on the Hamilton Scale demonstrated a difference between the treatment subsamples at the 5% level in favour of maprotiline with regard to gastro-intestinal symptoms on the 3rd day of treatment, and for late insomnia on the 21st day of treatment; however, amitriptyline improved the afternoon diurnal variation on the 21st day of treatment.

ONSET OF DRUG EFFECT

Cumulative frequencies and proportions of cases who were observed to respond to treatment after the 2nd day are reported in Table IV. The differences are in favour of maprotiline until the 20th day, but are particularly large from the 4th to the 7th day. The largest difference which is also significant in the Kolmogorov-Smirnov 2-sample test, is in fact observed on the 5th and 6th day when the 61,9% and 66,7% of cases on maprotiline, and 15% and 20%, respectively, of those on amitriptyline, demonstrated the effect of treatment.

TOLERABILITY

Over-all assessment of tolerability at the end of treatment did not show a significant difference between the 2 treatment groups. In 72% of the total sample (confidence limits: 59,18 - 82,85) there were either no side-effects recorded, or, if they appeared, they did not interfere with the patient's function.

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

Days of treatment	Maprotiline		Amitriptyline		Both treatments	
	No.	%	No.	%	No.	%
1	—	—	—	—	—	—
2	1	4,76	—	—	1	1,64
3	7	33,33	3	15,00	10	16,39
4	12	57,14	3	15,00	15	24,59
5	13	61,90	3	15,00	16	26,23
6	14	66,67	4	20,00	18	29,51
7	15	71,43	6	30,00	21	34,43
8	15	71,43	8	40,00	23	37,70
9	15	71,43	10	50,00	25	40,98
10	17	80,95	11	55,00	28	45,90
11	18	85,71	11	55,00	29	47,54
12	18	85,71	11	55,00	29	47,54
13	18	85,71	12	60,00	30	49,18
14	19	90,48	16	80,00	35	53,38
15	19	90,48	16	80,00	35	53,38
16	19	90,48	16	80,00	35	53,38
17	19	90,48	17	85,00	36	59,02
18	19	90,48	17	85,00	36	59,02
19	19	90,48	17	85,00	36	59,02
20	20	95,24	20	100,00	40	65,57
21	21	100,00			61	100,00
22 - 28						
	(2 cases not reported)		(2 cases not reported)			

Signs and symptoms elucidated by means of a check-list demonstrated a statistically significant difference in signs of rigidity, which were found to be more common among the maprotiline-treated patients, and tachycardia, which was found more frequently in the amitriptyline subsample. These differences were significant at the 5% level.

Six did not complete the trial; 2 discontinued taking maprotiline of their own accord because of remission, and the other 4 were equally distributed in the amitriptyline and maprotiline subsamples. One patient in the amitriptyline subsample had his medication suspended because of the development of a toxic confusional state and a second because of severe hypotension. Maprotiline was suspended in 2 patients, for headache in one, and headache and a dry mouth, in the other.

DISCUSSION

Maprotiline's rapid onset of action demonstrated by Pinto *et al.*,[3] Guz[5] and Grüter,[6] and confirmed in this study is particularly desirable in endogenous depression when suicide is an ever-present risk.

This study showed maprotiline to be effective in both agitated and retarded patients, demonstrating the bipolar nature of the drug's effect,[3,6] which is only observable clinically, and is very difficult to explain in pharmacological terms.

CONCLUSION

Over-all assessment demonstrated that 91% of the patients on maprotiline improved markedly or moderately, and that 64% improved to the same extent on amitriptyline after 4 weeks' treatment.

With regard to special symptoms, maprotiline significantly improved gastro-intestinal symptoms and late insomnia, on days 3 and 21, respectively, and amitriptyline significantly improved diurnal variation p.m. on day 21; these differences possibly occurred by chance.

Of the total of 110 assessments made, maprotiline was favoured 57 times (52%), amitriptyline 39 times (35%) and there were 14 ties (13%).

The onset of drug effect was significantly quicker in the maprotiline group compared with the amitriptyline group. By the 4th day of treatment 57% of the maprotiline group were recovering from their depressive illness, whereas only 15% of those on amitriptyline demonstrated the same improvement.

By the 6th day the differences in onset between the 2 antidepressants were even greater, with two-thirds of the maprotiline group showing onset of antidepressant effect, against one-fifth of the amitriptyline group.

The assessment of tolerability did not demonstrate any significant difference between the maprotiline and amitriptyline groups, although there was a trend in favour of maprotiline.

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