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A SEQUENTIAL DOUBLE-BLIND CONTROLLED STUDY OF MOCLOBEMIDE AND MIANSERIN IN ELDERLY DEPRESSED PATIENTS

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SUMMARY

Moclobemide was compared with mianserin in a double-blind controlled study in elderly depressed patients. Sequential analysis of 11 pairs of patients found no significant difference between the drugs at the week 8 analysis. Unpaired comparison of the 26 patients completing four weeks' treatment also showed no significant difference between the two drugs. Both drugs significantly reduced Hamilton and Carroll depression rating scores. A separate analysis of the 20 patients completing eight weeks' treatment showed that both drugs produced significant decreases in Hamilton and Carroll depression ratings with no significant difference between the two drugs for depression scores at either week 4 or 8. Side-effects were minimal, with the most severe emergent side-effects for moclobemide being sleep disturbance, blurred vision and dry mouth.

KEY WORDS—Moclobemide, mianserin, elderly, depression.

INTRODUCTION

Depressive illness is the most common psychiatric condition found in the elderly (Blazer and Williams, 1980). The treatment of depression in the elderly has not been studied extensively although recent reports suggest that a response rate of 60–70% can be achieved with pharmacological treatments (Georgotas *et al.*, 1983, 1986). The tricyclic antidepressants have, until now, been the drugs of choice but have side-effects that may cause problems in the aged. These include sedative effects; anticholinergic effects including dry mouth, blurred vision, constipation, urinary retention; central anticholinergic effects such as mild memory loss, disorientation, confusional reactions; cardiovascular effects such as orthostatic hypotension and slowing of cardiac conduction; and the tricyclics are potentially fatal on overdose (Peabody *et al.*, 1986).

The 'second-generation' antidepressants do not offer any advantages in therapeutic efficacy but have fewer cardiovascular and anticholinergic side-effects than the tricyclics. Mianserin in particular has been shown to be effective in the treatment of elderly depressed patients (Eklund *et al.*, 1985) and has become commonly used in this country for elderly depression. The major drawback to the use of mianserin is the risk of blood disorders such as agranulocytosis to which the elderly may be more susceptible (Bateman *et al.*, 1988).

Reports of successful treatment of depression in the elderly using monoamine oxidase inhibitors (MAOIs) have led to renewed interest in these agents (Ashford and Ford, 1979; Georgotas *et al.*, 1983, 1986). The MAOIs are less cardiotoxic, less sedative, and have fewer anticholinergic side-effects than the tricyclic and 'second-generation' antidepressants (Peabody *et al.*, 1986). The possibility of a hypertensive crisis is the major problem with the MAOIs but new, safer MAOIs have been developed. Moclobemide, a benzamide, is a selective monoamine oxidase A inhibitor with fewer tyramine pressor effects than other MAOIs (Tiller *et al.*, 1987). A further advantage is the reversibility of moclobemide's inhibitory action, allowing surgery or the use of other drugs within 24 hours after cessation of treatment.

Moclobemide has been shown to be an effective antidepressant in open and double-blind placebo-controlled trials (Stefanis *et al.*, 1982; Cassacchia *et*

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al., 1984). Moclobemide has also been found to have comparable antidepressant efficacy to amitriptyline (Norman *et al.*, 1985), clomipramine (Larsen *et al.*, 1984) and desipramine (Stefanis *et al.*, 1984). Only one study of moclobemide in elderly patients has been reported (Postma and Vranesic, 1985). This was an open study in patients with both depression and dementia, and reported improvement in all patients at a dosage of 150–225 mg/d. The present study was undertaken to examine the efficacy of moclobemide in elderly patients with major depression. A double-blind paired sequential design was followed where moclobemide was compared to mianserin after four and eight weeks of treatment. In addition, an unpaired analysis comparing the antidepressant and anxiolytic properties and side-effects of the drugs was carried out after one, four and eight weeks of treatment.

METHODS

Patients

Inpatients or outpatients at The Royal Melbourne Hospital who met the DSM-111 criteria for major depressive episode and were aged 60 years or over were considered for the study. A score of >16 on the Hamilton Depression Rating Scale (Hamilton, 1960) after >7 days drug-free was required for admission to the study. Patients meeting the above criteria were entered in the study after giving informed consent according to the National Health and Medical Research Council Guidelines.

Assessments

Changes in depression and anxiety symptoms were assessed using the following observer rating scales: Hamilton Depression Rating Scale (HDRS), (Hamilton, 1960); Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959); and self-rating scales: Carroll Depression Rating Scale (CDRS) (Carrol *et al.*, 1981) and Speilberger State–Trait Anxiety Inventories (STAI–X_1 and STAI–X_2) (Speilberger *et al.*, 1970). Ratings were effected at baseline and at weeks 1, 4 and 8. A side-effects checklist (S–E) was completed at the same times. A Newcastle score was also recorded at baseline (Holden, 1983).

At the start of the study the following pathology tests were carried out: full blood examination, urea and electrolytes, liver function, thyroid function, electrocardiogram (ECG), dexamethasone suppression test, blood pressure and heart rate. All tests except the ECG were repeated at weeks 4 and 8.

Study design

A double-blind sequential trial with paired patients was carried out. Patients were paired according to sex, age (±5 years) and HDRS (±5 points) and allocated to treatment by one of the authors (KM) who was not involved in clinical assessments. Those patients who were not matched immediately were allocated to treatment on a random basis and matched with the next suitable patient. All patients followed standard MAOI dietary and medication restrictions.

Following a drug-free week, an initial total daily dose of moclobemide of 150 mg or mianserin of 30 mg was started on a three times a day schedule. Maximum daily doses allowed were 600 mg for moclobemide and 90 mg for mianserin. Nitrazepam 5–10 mg nocte was permitted as a hypnotic for any patient if required.

Analysis of results

The analysis of results was carried out using a skew restricted, repeated significance tests (RST) sequential plan (Armitage, 1975). The dimensions of the plan were set as α=0·90, power at 0·95 and an overall significance of 0·05. Preferences for either drug were decided based on changes in HDRS scores, a decrease of eight points being considered a clinical improvement as in previous studies (Norman *et al*, 1985). Ties were not recorded on the plan and separate analyses were done at weeks 4 and 8.

In addition, the two drug groups were compared at baseline, weeks 1, 4 and 8 using Student's *t*-tests.

RESULTS

Sequential analysis

Of the 41 patients who entered the study, 26 completed four weeks' treatment. Of these, 11 could be paired for the sequential analysis (this included one pair with an HDRS difference of six). There were 18 females and four males with ages ranging from 60 to 83 years, with the mean for each group shown in Table 1. Baseline ratings for the two

Table 1. Baseline (week 1) age, Newcastle score, HDRS, CDRS, HARS, STAI-X_1, STAI-X_2 and S-E scores for the 11 pairs of patients analysed by the sequential method

	Moclobemide		Mianserin			
	Mean	S.D.	Mean	S.D.t	t	p
Age	69·9	5·4	69·6	6·4	0·11	0·915
Newcastle	6·4	1·3	6·6	2·7	0·30	0·766
HDRS	25·0	5·8	26·5	3·3	0·76	0·454
CDRS	30·8	8·9	30·1	8·7	0·19	0·848
HARS	17·5	5·9	18·7	8·5	0·41	0·687
STAI-X_1	60·4	11·7	66·1	15·1	1·00	0·331
STAI-X_2	58·9	12·1	62·2	12·3	0·63	0·537
S-E	8·1	3·1	9·0	3·2	0·66	0·519

groups were not significantly different (Table 1). At week 4, there were four wins for moclobemide, two wins for mianserin and the number of tied results was five, thus the plan did not reach any of the boundaries (Fig. 1). At week 8, the plan reached the no significant difference boundary (Fig. 2). The results for the 11 pairs included three wins for moclobemide, four wins for mianserin and four ties.

Unpaired comparison of drug groups

The 26 patients (13 on each drug) who completed four weeks' treatment were compared at baseline, week 1 and week 4. The mean age (SD) for the moclobemide group was 69·7 (6·0) and for the mianserin group 69·5 (6·9). Mean Newcastle scores were 6·3 (1·3) for moclobemide and 6·4 (2·6) for mianserin. There were no significant differences between the two groups in mean age (t = 0·06, p=0·952), Newcastle score (t = 0·14, p = 0·892), HDRS, CDRS, HARS, STAI-X_1, STAI-X_2 or S-E ratings at baseline (Table 2). There were no significant differences between the two groups for any of the ratings at either week 1 or week 4 (Table 2).

In the moclobemide group, the HDRS and CDRS ratings decreased significantly from baseline to week 1 (Table 2). All ratings except STAI-X_2 decreased significantly from baseline to week 4 in the moclobemide group. In the mianserin group, the HDRS, CDRS and HARS ratings decreased significantly from baseline to week 1 (Table 2). All ratings except STAI-X_2 and S-E decreased significantly from baseline to week 4. (Table 2).

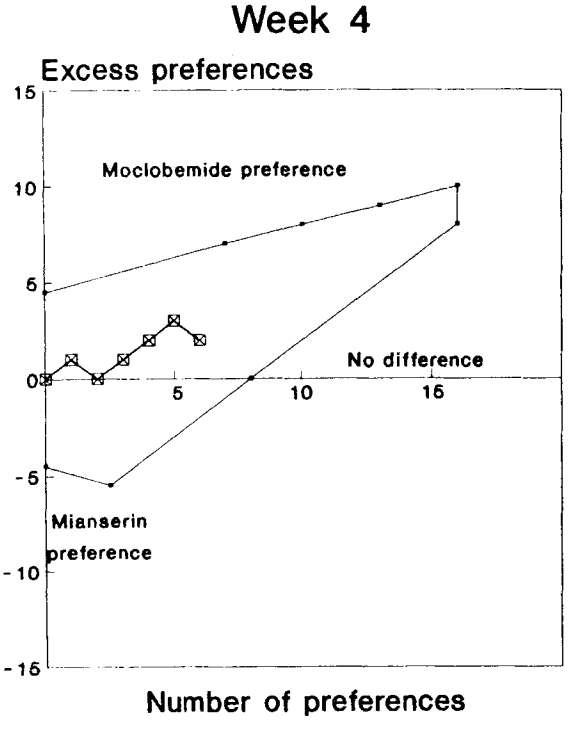

Fig. 1. Sequential analysis of moclobemide and mianserin at week 4.

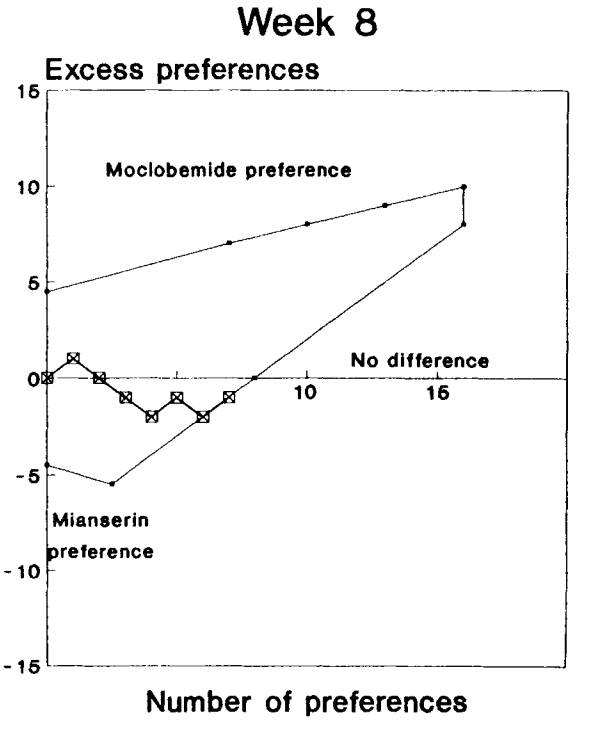

Fig. 1. Sequential analysis of moclobemide and mianserin at week 8.

Table 2. HDRS, CDRS, HARS, STAI-X_1, STAI-X_2 and S-E scores for the 26 unpaired patients (n = 13 in each group) completing week 4. t, Student's t; from baseline [a]p <0·05, [b]p <0·01, [c]p <0·005, [d]p <0·001

	Week	Moclobemide Mean	SD	Mianserin Mean	SD	t	p
HDRS	0	25·8	5·8	25·2	4·6	0·34	0·738
	1	21·4[a]	7·5	20·1[a]	7·7	0·44	0·664
	4	15·0[d]	8·7	16·8[b]	9·1	0·51	0·616
CDRS	0	31·3	8·3	27·8	10·0	0·98	0·335
	1	26·8[a]	8·2	23·0[a]	8·7	1·14	0·267
	4	21·8[b]	13·0	19·2[c]	12·1	0·55	0·589
HARS	0	18·7	6·6	18·2	7·9	0·19	0·851
	1	16·5	9·3	15·4[b]	6·7	0·34	0·737
	4	11·4[d]	6·8	13·2[a]	8·1	0·63	0·534
STAI-X_1	0	60·8	11·6	62·5	16·9	0·27	0·769
	1	59·5	14·5	57·7	17·1	0·27	0·788
	4	52·1[a]	17·9	51·5[a]	19·9	0·08	0·935
STAI-X_2	0	57·8	11·9	58·7	15·6	0·17	0·867
	1	58·5	10·1	57·5	14·1	0·19	0·849
	4	50·9	16·1	51·9	18·3	0·15	0·886
S-E	0	9·1	3·8	8·6	3·2	0·38	0·711
	1	7·7	4·6	8·0	2·7	0·21	0·837
	4	6·5[a]	4·9	7·8	4·8	0·73	0·474

Table 3. HDRS, CDRS, HARS, STAI-X_1, STAI-X_2 and S-E scores for the 20 (moclobemide n □ 11, mianserin n = 9) unpaired patients completing week 8. t, Student's t; from baseline [a]p <0·05, [b]p <0·01, [c]p <0·005, [d]p <0·001

	Week	Moclobemine Mean	SD	Mianserin Mean	SD	t	p
HDRS	0	25·1	6·0	25·2	5·3	0·05	0·960
	1	20·6	7·8	19·9[a]	7·8	0·21	0·834
	4	13·0[d]	7·8	12·4[c]	7·2	0·16	0·872
	8	11·5[c]	6·9	7·6[d]	6·1	1·35	0·194
CDRS	0	29·8	8·2	25·1	11·0	1·10	0·381
	1	25·1[a]	7·3	21·9	9·8	0·84	0·365
	4	18·9[b]	11·8	13·2[c]	9·0	1·19	0·249
	8	18·1[c]	10·6	7·9[d]	7·1	2·44	0·024
HARS	0	18·2	6·6	17·6	8·5	0·19	0·855
	1	15·9	9·1	15·2	5·5	0·20	0·845
	4	10·4[d]	6·5	9·9[b]	7·1	0·16	0·877
	8	10·5[a]	7·1	5·8[c]	4·7	1·73	0·102
STAI-X_1	0	58·4	10·9	59·7	18·3	0·20	0·846
	1	58·2	15·5	55·4	19·0	0·35	0·727
	4	50·5[a]	17·9	44·0[b]	19·0	0·78	0·445
	8	48·9[a]	17·1	35·4[c]	13·6	1·96	0·071
STAI-X_2	0	55·3	11·2	57·3	17·5	0·32	0·753
	1	57·5	10·8	54·7	14·9	0·50	0·622
	4	49·3	15·8	43·6[c]	15·2	0·82	0·424
	8	50·7	17·5	38·8[a]	14·9	1·62	0·122
S-E	0	8·8	4·3	7·6	3·0	0·72	0·479
	1	7·5	4·9	7·9	2·3	0·26	0·799
	4	6·1	5·2	5·8[a]	2·9	0·16	0·874
	8	5·3[a]	3·8	4·3[b]	4·0	0·53	0·601

A separate analysis of the 20 patients who continued to eight weeks was carried out. Eleven patients were on moclobemide and nine on mianserin (two mianserin dropouts were included in the sequential design hence the 22 patients for that week 8 analysis). The mean age for the moclobemide group was 68·8 (6·0) and for the mianserin group 68·8 (8·1). Mean Newcastle scores were 6·2 (1·3) for moclobemide and 6·6 (2·1) for mianserin. There were no significant differences between the two groups in mean age (t □ 0·01, p □ 0·990), Newcastle score (t = 0·57, p = 0·576), HDRS, CDRS, HARS, STAI-X*1*, STAI-X_2, or S-E ratings at baseline (Table 3). There were no significant differences between the two groups for any of the ratings at either week 1 or week 4 (Table 3). The only significant difference found between the drug groups at week 8 was in the CDRS ratings, where the mianserin group had a significantly lower CDRS (Table 3).

In the moclobemide group, the CDRS ratings decreased significantly from baseline to week 1, while all ratings except STAI-X_2 and S-E decreased significantly from baseline to week 4. All ratings except STAI-X_2 decreased significantly from baseline to week 8 (Table 3). For the mianserin group, the HDRS ratings decreased significantly from baseline to week 1, while all ratings decreased significantly from baseline to week 4 and to week 8 (Table 3).

Drug dosages

For the 26 patients completing four weeks' treatment, the mean dosages at week 4 were 412 (74) mg/d for moclobemide and 85 (13) mg/d for mianserin. For the 20 patients completing eight weeks, the mean dosages at both week 4 and 8 were 405 (79) and 450 (95) for moclobemide, and 87 (10) and 90 (0) mg/d for mianserin respectively.

Side-effects

Both drugs were well tolerated and side-effects were minimal. The number of reported side-effects decreased during the study for both drugs (see Tables 2 and 3). There were no major adverse effects requiring dose reduction or cessation of treatment with either drug. The treatment emergent side-effects (side-effects not present prior to commencement of treatment) which were rated by the patients as severe at either week 4 or 8 were, for the moclobemide group, sleep disturbance (one patient), blurred vision (one patient) and dry mouth (one patient); and for the mianserin group, dry mouth (three patients), physical tiredness (one patient), micturition effects (one patient), constipation (one patient) and orthostatic effects (one patient). This was not a significant difference in distributions (chi-squared = 1·46, p = 0·227).

There were no biochemical or haematological abnormalities detected before or during treatment. This provides safety data for 96 patient weeks for moclobemide and 88 patient weeks for mianserin.

Dropouts

None of the 15 dropouts or exclusions were related to adverse medication effects. Five were due to non-cooperation or non-attendance, one patient was withdrawn following a suicide attempt, five had exacerbations of other physical illnesses, and four patients were excluded due to missing data. Six of the dropouts were on moclobemide and eight were on mianserin, not a significant difference in distributions. There were no significant differences in age or in baseline HDRS ratings for these 15 patients as compared to the 26 patients who completed four weeks of treatment. Six patients did not continue after week 4 due to failure to respond to treatment; four patients were on mianserin and two on moclobemide.

DISCUSSION

In previous open and controlled studies, moclobemide has been shown to be an effective antidepressant comparable to other established antidepressants. In the present study of depression in the elderly, moclobemide was shown to be not significantly different to mianserin both by paired sequential analysis and by unpaired statistical comparison.

An earlier onset of action was evident for moclobemide in this study in comparison to our previous study of moclobemide in atypical depression (Tiller *et al.*, 1988). In the current study, both HDRS and CDRS ratings were significantly decreased at week 1 in the patients who completed four weeks and the CDRS ratings were significantly reduced at week 1 in the eight-week group. Significant reductions in HDRS ratings after one week of 300 mg/d moclobemide have also been shown in patients with moderate–severe unipolar and bipolar depression (Lensch *et al.*, 1987).

Both drugs showed significant decreases in HDRS and CDRS ratings from baseline to weeks 4 and 8. Both drugs showed significant decreases in mean HARS scores from baseline to weeks 4 and 8. Mianserin significantly reduced the trait scale (X_2) of the STAI in the patients who continued to week 8, while the subject-rated state scale of the STAI (X_1) was significantly decreased by both drugs at weeks 4 and 8.

Both drugs were well tolerated and mean side-effects scores fell significantly during treatment. No adverse events were reported and in particular, no problems with postural hypotension nor hypertensive episodes were noted. Moclobemide was not associated with changes in biochemical or haematological parameters during the study, consistent with other safety data to date (Norman *et al.*, 1985; Tiller *et al.*, 1989). None of the dropouts were due to adverse drug effects.

This is the first double-blind controlled study of moclobemide in elderly patients with depression. Since the study did not include a placebo, it cannot be definitively concluded that moclobemide has antidepressant activity in this group. However, significant decreases in both observer and subject ratings of severity of depression were found in the patients treated with moclobemide.

Moclobemide, with its greater safety than conventional MAOIs, may provide a new agent for the treatment of geriatric depression. The present study was carried out with standard MAOI dietary restrictions but recent reports suggest that this is not necessary as long as the drug is taken at mealtimes (Roche Investigational Drug Brochure). This would also be a further advantage in the elderly, who are often institutionalized or in nursing homes. The rapid onset of antidepressive action shown in this study, if confirmed in a larger study, would be a significant advance over the tricyclic antidepressants. This is particularly important in the elderly as they have a higher risk of suicide than younger patients (Bridges, 1986).

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