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Moclobemide Versus Clomipramine in Endogenous Depression

A Double-Blind Randomised Clinical Trial

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The effects of moclobemide (300–600 mg/day), a reversible monoamine oxidase inhibitor – A (MAOI-A), were compared in a double-blind, multi-centre trial with those of clomipramine (100–200 mg/day) on 129 in-patients suffering from endogenous depression (according to ICD-9 and the Newcastle Scale). No significant differences in efficacy were seen between the two treatment groups. In the moclobemide group the mean scores on the MADRS were 36.4 on day 0 and 13.2 on day 42 (end-point analysis); scores were 37.4 and 10.9 respectively in the clomipramine group. An earlier onset of antidepressant activity was noted for moclobemide. Tolerability was significantly better for moclobemide, as shown by the Clinical Global Impression of Tolerance (CGI_T). Anticholinergic effects, weight gain and orthostatic hypotension were more frequent in the clomipramine group. No biological treatment-related changes were observed.

Moclobemide, a benzamide derivative, is a new monoamine oxidase inhibitor (MAOI) which predominantly inhibits the A form of MAO and is characterised by the fact that its MAO binding is reversible (Burkard *et al*, 1989; Da Prada *et al*, 1989).

Pharmacodynamic studies have suggested that, compared with irreversible MAOIs such as tranylcypromine (Berlin *et al*, 1989), moclobemide is a safe drug with respect to potentiation of the action of tyramine. Moclobemide has been used safely in therapeutic trials without dietary tyramine restriction.

Double-blind comparative clinical trials have shown that the efficacy of moclobemide was superior to placebo (Casacchia *et al*, 1984) and comparable to the following tricyclic compounds: clomipramine (Larsen *et al*, 1984), amitriptyline (Norman *et al*, 1985), desipramine (Stefanis *et al*, 1984), and imipramine (Baumhackl *et al*, 1989; Versiani *et al*, 1989). Moclobemide was tolerated better than tricyclics with regard to anticholinergic symptoms and cardiovascular effects.

The objective of this study was to compare the efficacy and tolerability of moclobemide and clomipramine in the treatment of endogenous depression in an in-patient population.

Method

This was a double-blind, prospective clinical trial, conducted in 13 French psychiatric departments (see footnote). Two randomised parallel groups of patients were treated with either moclobemide or clomipramine. The study's drug administration period was six weeks, immediately following a wash-out period of at least three days (15 days if the patient was being treated with a MAOI before the study).

Those eligible for the study were patients admitted to hospital for an endogenous depression, according to ICD-9 (296.1/296.3) (World Health Organization, 1978) and the Newcastle Scale (Roth *et al*, 1983). In addition they were to fulfil DSM-III criteria for a major depressive episode (American Psychiatric Association, 1980). A total score of 25 or more on the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery *et al*, 1979) at the end of the wash-out period was also required. Subjects were aged between 18 and 65.

The study was carried out in accordance with the Declaration of Helsinki: patients were included after giving informed consent and the protocol was approved by an ethical committee. Patients whose suicidal risks were such that actual urgent treatment was justified (sedative neuroleptics, ECT) were excluded from the study, as were those who presented any of the following: evidence of psychosis, a confusional state, drug or alcohol abuse, severe organic disorders, pregnancy, or lactation. Patients with contraindications for clomipramine and those with foreseeable poor compliance were also excluded.

Patients received capsules, identical in appearance, containing either 75 mg moclobemide or 25 mg clomipramine. Two capsules were to be taken three times per day after meals.

From day 1 to day 14, moclobemide was given at a fixed daily dose of 450 mg (6 capsules – 2 in the morning, 2 at noon, 2 in the evening). From day 1 to day 5, the daily dose of clomipramine was increased progressively from 75 mg (placebo was added to make up 6 capsules) to 150 mg. The dose of 150 mg was maintained until day 14. If the patient suffered from side-effects, the dosage was reduced at day 7 by one capsule to 375 mg moclobemide or 125 mg clomipramine. On day 15, depending on tolerability and efficacy, the daily dosage could be reduced to 300 mg moclobemide or 100 mg clomipramine (4 capsules).

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or increased to a maximum of 600 mg moclobemide or 200 mg clomipramine (8 capsules). Generally, the dose administered on day 15 was maintained until day 42.

In cases of severe anxiety, diazepam (5–30 mg daily) could be given (i.v. or by mouth during the wash-out period). In case of insomnia, 1000–3000 mg chloral hydrate at night could be prescribed. Lithium could be continued if it had been given for at least three months before the trial. Anethole trithione was also permitted at a dose of 4–6 tablets per day in cases of dry mouth.

Drugs which had been given chronically for somatic complaints were continued if they did not have any psychotropic effect. As far as possible, such concomitant treatment was maintained at a constant dose level during the study. No medications forbidden with classical MAOIs were allowed in this trial.

Assessments were made at baseline (day 0), and on days 3, 7, 14, 21, 28 and 42 of treatment. The efficacy of moclobemide and clomipramine was measured by means of three rating scales: the MADRS was completed at each clinical evaluation (raters were trained before the trial was started in order to obtain homogeneous ratings); the Hamilton Rating Scale for Depression (HRSD, 21 items) (Hamilton, 1960, 1967) was completed at baseline and at the end of the study; a Clinical Global Impression of Efficacy (CGI_E), using four gradings, was given by the investigator at the end of the study. Patients completed the Symptom Check List (SCL-90R) (Derogatis, 1977) on day 0 and at the end of the study.

Safety was assessed as follows: clinical examination, ECG and laboratory tests on blood and urine were performed at baseline and at the end of the study. Supine and standing blood pressure (BP), heart rate, and a check-list of somatic symptoms (CHESS) (Guelfi *et al*, 1983) were recorded at each clinical evaluation. BP in the supine position was recorded after a rest of five minutes; BP in the erect position was recorded immediately after orthostatism and one minute later. BP had to be taken from the same arm, 30 minutes to one hour after breakfast. The CHESS investigated 68 items scored from 0 to 4. A Clinical Global Impression of Tolerance (CGI_T), using four gradings, was given by the investigator at the end of the study.

Statistical methods

Quantitative variables were described by the usual parameters: mean, standard deviation, range. Each qualitative variable was expressed in terms of percentage or absolute frequencies. Analysis of variance (ANOVA) or covariance (ANCOVA) (using day 0 as a covariate) for repeated measurements was used to compare efficacy and safety parameters in the two treatment groups (Winer, 1971). When parametric models were not adequate, the Mann-Whitney test was used to compare the two groups. The qualitative data of the two groups were compared with a χ^2 test. The level of statistical significance was fixed at 5%. The calculations were made with the BMDP statistical package (Dixon, 1985).

Results

Of the 135 patients screened, six were excluded from all statistical analysis owing to non-compliance with the protocol (unrelated to treatment). Four were from the moclobemide group: two left hospital, one was an out-patient from the beginning of the trial, one had seizures on the third treatment day (alcoholism, seizures from alcohol withdrawal). Two were from the clomipramine group: one had hypertensive episodes which were present before the study began, and one was discovered to have Wolff-Parkinson-White syndrome on ECG at baseline.

Therefore, 129 in-patients with a diagnosis of endogenous depression were included for the evaluation of efficacy and tolerability. There were 62 in the moclobemide group and 67 in the clomipramine group. The comparability of the two groups after randomisation was verified according to age, sex, diagnosis and severity of depression on the MADRS and HRSD (Table 1).

A total of 26 patients withdrew from drug treatment. There were 24% ($n = 15$) in the moclobemide group (m) and 16% ($n = 11$) in the clomipramine group (c), the most frequent reasons being: inefficacy ($n_m = 10$, $n_c = 4$), side-effects ($n_m = 2$, $n_c = 5$), hypomanic or manic swing ($n_m = 2$, $n_c = 1$). The reasons for premature termination were not statistically different in the two treatment groups. The efficacy and tolerability data of these patients were taken into account as they had all stopped taking the study drug on or after the 14th day of the study.

Modifications to treatment during the trial were studied by comparing the number of capsules used at the start and at the end of treatment. In the moclobemide group, 69% of patients ($n = 43$) were still receiving the initial dosage at the end of treatment, 21% ($n = 13$) were receiving an increased dosage, and 10% ($n = 6$) were receiving a reduced dosage. In the clomipramine group, for 73% of patients ($n = 49$) the dosage had not changed by the end of treatment, for 13.5% ($n = 9$) it had been increased and for 13.5% ($n = 9$) it had been reduced. These percentages were similar among only those who withdrew from the study. The highest daily mean dosages were 476 mg on days 19 and 21 for moclobemide, and 156 mg on days 16 and 18 for clomipramine. The mean daily dosages over the entire trial period were 462 mg moclobemide and 146 mg clomipramine.

Table 1
Baseline demographic and illness characteristics of 129 endogenous depressive patients randomly allocated to either moclobemide ($n = 62$) or clomipramine ($n = 67$) treatment

	Moclobemide	Clomipramine
Mean (s.d.) age: years	46.5 (13.3)	47.7 (11.4)
range	19.7–65.1	19.4–66.9
Sex		
males	21	19
females	41	48
No. of patients with:		
monopolar endogenous depression	56	62
bipolar endogenous depression	6	5
Mean (s.d.) total MADRS score	36.4 (6.0)	37.4 (6.6)
Mean (s.d.) total score on first 17 items of the HRSD	27.3 (4.4)	27.7 (5.1)

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Table 2
MADRS scores and investigator's overall assessments of efficacy (CGI_E)

	Moclobemide		Clomipramine	
	All patients[1]	Completers[2]	All patients[1]	Completers[2]
MADRS scores: mean (s.d.)				
days of assessment				
0	36.4 (6.0) ($n=62$)	36.2 (5.5)	37.4 (6.6) ($n=67$)	37.0 (6.5)
3	32.9 (8.3) ($n=61$)[3]	31.7 (7.8)	34.4 (7.1) ($n=66$)[3]	34.0 (6.7)
7	26.8 (9.8) ($n=62$)	25.5 (9.5)	30.0 (7.9) ($n=67$)	28.9 (7.8)
14	20.3 (10.3) ($n=62$)	16.9 (6.4)	22.2 (9.2) ($n=67$)	20.2 (7.8)
21	14.4 (10.3) ($n=60$)	10.6 (5.3)	16.0 (9.6) ($n=66$)	13.9 (6.2)
28	11.2 (8.5) ($n=53$)	9.3 (6.2)	10.9 (7.0) ($n=61$)	10.8 (6.9)
42[4]	8.1 (7.1) ($n=47$)		8.0 (7.5) ($n=56$)	
Final score[5]	13.2 (12.9) ($n=62$)		10.9 (11.6) ($n=67$)	
CGI_E				
very good	39.3% ($n=24$)		40.3% ($n=27$)	
good	26.2% ($n=16$)		31.3% ($n=21$)	
moderate	18.1% ($n=11$)		17.9% ($n=12$)	
none or worsening	16.4% ($n=10$)		10.5% ($n=7$)	
not assessed	- ($n=1$)		- -	

1. All patients over the treatment period.
2. Patients having gone through the whole trial.
3. Data missing for one patient.
4. MADRS mean (s.d.) and number of patients are the same for 'all patients' and 'completers'.
5. Endpoint of all included patients.

There were no statistically significant differences between the two study groups with regard to prescription of concomitant medication for anxiety and insomnia. On day 14, diazepam was given to 55% of moclobemide patients and 67% of clomipramine patients. Chloral hydrate was given to 37% of moclobemide patients and 41% of clomipramine patients. After day 14 these prescriptions gradually decreased, the ratios between the two treatment groups remaining similar. Five patients in the moclobemide group and two in the clomipramine group continued existing lithium treatment throughout the study period.

Concomitant medication for treatment of symptoms of the digestive tract consisted mainly of treatment for severe cases of dry mouth and constipation. Anethole trithione was given to 3% of moclobemide patients and 13% of clomipramine patients. Only patients in the clomipramine group used laxatives (10%). Prescription for other signs and symptoms was minimal. Pressor drugs were not allowed in the study; it should be noted, however, that six patients in the clomipramine group were treated with heptaminol or dihydroergotamine and one patient of the moclobemide group with theodrenaline which was used safely. These comedications were considered as a minor protocol deviation.

The mean total score on the MADRS showed a steady decline in both study groups (Table 2). The analysis of covariance for repeated measurements including data until day 14 (there were no drop-outs in this period) showed a significant day effect ($P<0.0001$). After day 14, the comparison of the means of the two treatments using Student t-tests and Bonferroni criteria showed no significant difference at days 21, 28, and 42. Furthermore, the means (s.d.) of reduction between day 0 and the final scores on the MADRS (day 42 or the last day of treatment) were not statistically different ($P=0.13$) for moclobemide (23.2 (12.8)) and for clomipramine (26.6 (12.4)). The 95% confidence intervals (CI) of the difference between the mean MADRS reduction scores of the two treatment groups, i.e. moclobemide − clomipramine (−3.4), was [−7.8; +0.9], showing a study power of approximately 40%.

The means of MADRS global scores at each time point for the 103 patients having gone through the whole trial are given in Table 2. A variance analysis with two factors (treatment and day) on the seven times of measurement showed a significant day effect ($P<0.0001$) and a significant treatment effect ($P<0.05$) in favour of moclobemide with $P<0.01$ at days 7, 14, and 21. On the last assessment at day 42 the scores obtained were quite close.

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Table 3
SCL-90R global scores and three factorial scores (mean (s.d.))

	Moclobemide	Clomipramine
Global score		
baseline	110.0 (51.5) (n=45)	121.9 (54.7) (n=52)
final	60.6 (73.0) (n=50)	53.0 (45.1) (n=45)
Depression		
baseline	49.1 (19.2) (n=52)	50.2 (21.1) (n=57)
final	22.5 (24.1) (n=53)	22.6 (20.3) (n=53)
Somatisation		
baseline	12.7 (9.8) (n=55)	16.0 (10.1) (n=58)
final	7.3 (11.2) (n=52)	7.8 (7.7) (n=53)
Panic agoraphobia		
baseline	4.9 (5.5) (n=57)	6.9 (6.5) (n=60)
final	3.3 (6.3) (n=53)	3.4 (4.7) (n=54)

n=number of patients assessed on each score at baseline and final point.

Table 4
Symptoms (CHESS) observed in decreasing order of frequency (⩾10%) and investigator's overall assessment of tolerance (CGI_T)

	Moclobemide: %	Clomipramine: %
Symptoms		
Dry mouth	6	43
Constipation	13	27
Dizziness	15	24
Intolerance to noise	23	13
Sweating	16	22
Weight gain	15	22
Bitter taste in mouth	11	21
Physical agitation or tension	18	13
Memory disturbances	18	9
Hot flushes	2	18
Cephalalgia	15	12
Sleepiness	11	15
Chilliness	8	15
Muscular pain	13	10
Blurred vision	6	13
CGI_T		
Very good	62.9% (n=39)	31.3% (n=21)
Good	24.2% (n=15)	35.8% (n=24)
Moderate	9.7% (n=6)	25.4% (n=17)
Poor	3.2% (n=2)	7.6% (n=5)

The decreases in the mean (s.d.) total scores (first 17 items) of the HRSD from day 0 to the end of treatment were not statistically different (P=0.3) for moclobemide (16.2 (10.3)) and clomipramine (18.1 (10.2)). The HRSD (21 items) also showed no statistical difference in the score reductions for the two treatment groups. The CGI_E given by the investigators was good or very good in 65.5% of moclobemide patients and in 71.6% of clomipramine patients. These results (Table 2) compared by a χ^2 test were not significant (χ^2=0.5, P=0.5).

The global score and the three factors of the SCL-90R which have shown stable factorial structure in a French sample (Pariente *et al*, 1989) - depression, somatic disorders and panic agoraphobia - were analysed (Table 3). No significant difference was found between the two treatment groups for the global and depression scores, either initially or at the end of the study. The scores for somatic and panic factors were initially higher in the clomipramine group, but the difference was not significant. The improvements assessed by the differences between the initial and final scores were not significant at P=0.05 except for the panic factor, for which the difference slightly exceeded the limit of significance with t=1.99 in favour of clomipramine, a difference which was essentially due to the difference in baseline scores: 6.9 for clomipramine subjects compared with 4.9 for moclobemide.

The investigators were asked to record the date of the beginning of an antidepressant or other therapeutic effect, if any, and the moment when the full antidepressant effect was observed. According to their findings, the antidepressant activity of moclobemide began significantly earlier (mean (s.d.) = 10 (5) days) than that of clomipramine (mean (s.d.) = 13 (5) days) (P<0.01). The maximum effect also occurred significantly earlier (P<0.02) with moclobemide (mean (s.d.) = 21 (8) days) compared with clomipramine (mean (s.d.) = 25 (8) days).

An 'activator' effect was also reported in 29 patients in the moclobemide group and 31 patients in the clomipramine group. It occurred significantly earlier in the moclobemide group (mean (s.d.) = 11 (7) v. 18 (7) days) (P<0.01). A sedative effect was reported in only 5% of patients in the moclobemide group compared with 18% in the clomipramine group (P<0.05). An anxiolytic effect was observed in 21% and 33% respectively (NS).

The adverse events which appeared during treatment with an incidence of ⩾10% of all patients, reported by means of a checklist (CHESS), are shown in Table 4. The items of the CHESS were grouped into 18 clinical clusters which seemed to have a clinical significance. The ANOVA for repeated measures showed a significant reduction from day 0 to day 14 (day effect of treatment) in the two treatment groups for 14 of the 18 clinical clusters, i.e. changes in appetite, digestive disorders, endocrine disorders, cephalalgia, cardiovascular signs, ENT disorders, sleep disorders, changes in vigilance, neuromuscular signs, cutaneous signs, memory disorders, hyperreactivity, pains, and changes in libido.

Anticholinergic side-effects were increased with clomipramine and reduced with moclobemide, and bucco-lingual signs were stable with moclobemide and increased with clomipramine.

The Mann-Whitney tests showed a difference between the two groups on days 7 and 14 in the incidence of digestive

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disorders, anticholinergic signs and bucco-lingual signs in favour of moclobemide. After day 14, this difference was still evident for bucco-lingual signs on days 21, 28 and 42, and was also significant on day 28 for anticholinergic symptoms and on day 42 for digestive disorders.

The mean heart rate did not show any significant changes in either group. The mean values of systolic blood pressure (SBP) showed a slightly larger decrease with clomipramine than with moclobemide. The difference between the means of the two groups did not seem to have any clinical significance.

The means of orthostatic changes based on the difference between supine and standing SBP were significantly lower for moclobemide than for clomipramine at days 7 ($P=0.02$), 14 ($P=0.02$) and 21 ($P=0.0008$). Orthostatic hypotension above 30 mmHg was almost only observed with clomipramine: 1 observation with moclobemide v. 16 in 10 patients on clomipramine. Five patients in the moclobemide group with normal BP values at baseline showed transitory increases to SBP > 160 mmHg, but this was not attributed by the investigators to any tyramine ingestion. Patients did not complain of headaches and BP returned to normal values at a subsequent check. No drug-induced changes towards abnormality were found on ECG in this study.

The weight means did not vary in the course of treatment in the moclobemide group (65.7 kg at the beginning of the study and 65.6 kg at the end). The weight means were, on the contrary, higher at the end of the trial (64.2 kg) in the clomipramine group than at the beginning of treatment (63.1 kg). The difference between the two treatment groups was significant ($P=0.001$).

The leucocyte count was found to be above 10 000/mm^3 in five patients receiving moclobemide treatment, and a slight and transient increase of transaminases (ASAT) was observed in one patient for whom moclobemide treatment was maintained. These modifications were considered to be of no clinical significance and to be unrelated to treatment.

Tolerance was judged to be very good or good in 87% of moclobemide patients and in 67% of clomipramine patients ($P=0.007$).

Overall assessment

The rates of 'success' and 'failure' of the treatments corroborated well with those of CGI efficacy. 'Success' was defined as a 50% or greater decrease in the total score and a final score below 20 on the MADRS, and in addition the exclusion of poor tolerance. Thus 68% of those treated with moclobemide and 75% of those on clomipramine were successes (NS).

Discussion

The present study was designed to evaluate the efficacy and tolerability of moclobemide in comparison with clomipramine, a standard tricyclic antidepressant. The crucial point in the assessment of efficacy of an antidepressant is still considered to be its efficacy in endogenous depression and in particular severe depressive syndromes (Commission of the European Communities, 1989). 'Endogenous depression' is a term which has been extensively debated (Andreasen *et al*, 1980, 1986) and which for practical reasons has been defined in this study according to ICD–9 and the Newcastle Scale.

Independently from different total scores on rating scales, hospital admission can be viewed as a solid parameter of severity and so this study was performed only in in-patients suffering from endogenous depression. Given these two conditions, this sample of 129 patients seems to be homogeneous enough to enable conclusions to be drawn with regard to efficacy and tolerability, although a larger number of patients would have increased the power of the study in detecting possible differences between moclobemide and clomipramine. However, the different results of this study and, in particular, the parallelism of the MADRS curves at any time point, speaks in favour of a strict equivalence of efficacy for both treatments.

The results of this specific trial were consistent with those of two other large multi-centre studies, conducted by Versiani *et al* (1989) and Baumhackl *et al* (1989), using the same daily dosage range of moclobemide compared with imipramine. It was shown that the proportion of responders on the HRSD was similar to that of this trial, with no difference with the tricyclic reference compound, in a sub-group analysis of patients with endogenous depression according to ICD–9. On the basis of these results, the antidepressant action of moclobemide can be recognised in endogenous depression, an indication which has been questioned for the first generation of MAOIs (British Medical Research Council, 1965; Paykel *et al*, 1989).

Furthermore, the onset of the antidepressant effect was judged to be more rapid for moclobemide than for clomipramine. It is possible that this earlier action may have arisen from the different dose schedules for the two drugs – a parallel increase in the dosage of clomipramine would have been contraindicated owing to the high prevalence of side-effects with this drug (Hollister, 1977).

The tolerability of moclobemide proved to be significantly better than that of clomipramine, particularly as regards anticholinergic effects and orthostatic hypotension. It should be noted that no dietary restrictions were given to the patients and that the few cases of transient elevation of SBP under moclobemide treatment had no relationship to any tyramine food ingestion. Therefore, these must be differentiated from the rise in blood pressure experienced by patients, even without headache, under treatment with first-generation MAOIs when given tyramine by mouth (Blackwell *et al*, 1967).

This was subsequently termed 'hypertensive crisis' and led to some discrediting of older irreversible MAOIs.

Conclusion

It was concluded that moclobemide, a reversible MAOI-A, combines safety and satisfactory efficacy in endogenous depression. The evidence of this trial shows moclobemide to be an effective and useful addition to the repertoire of drugs which can be employed for the treatment of this disorder. Although the efficacy of moclobemide and clomipramine were similar, it can be assumed that they exert their effects by different neurochemical pathways. In consequence, moclobemide is also worthy of consideration for treatment of the 30–35% of patients with endogenous and other severe depressions who fail to respond to both tricyclic compounds and other new antidepressants. An advantage is that treatment can be initiated immediately after completion of a trial with a tricyclic drug which has proved therapeutically ineffective, since adverse drug interactions do not occur (Puech *et al*, 1990).

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