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Moclobemide (Ro 11-1163) vs. Clomipramine in the Treatment of Depression: A Double-Blind Multicenter Study in Belgium

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ABSTRACT

Cattiez P.H., M. Dierick, B. Troisfontaines, L. van Audenrode, J. Defleur, W. Hermans, A. Roelandts, P. Stenier, and C. Wolfrum: Moclobemide (Ro 11-1163) vs. clomipramine in the treatment of depression: A double-blind multicenter study in Belgium. Drug Dev. Res. **21**:325–331, 1990.

A multicenter study to compare the antidepressant efficacy and the tolerance of moclobemide (Ro 11-1163) to clomipramine was performed in parallel groups of patients with minor depression. The duration of the study was 6 weeks, with weekly assessments by means of Hamilton Scale of Depression (HRDS) and the Clinical Global Impression (CGI). The efficacy of moclobemide was found to be as good as that of clomipramine. The results for tolerability were possibly in favor of moclobemide. It was recommended that consumption of tyramine-containing foods be kept to a minimum or avoided and no hypertensive crises were reported.

Key words: antidepressants, monoamine oxidase inhibitors, tyramine

INTRODUCTION

Irreversible inhibitors of monoamine oxidase (MAO) were the first drugs to be recognized as effective in the treatment of depression [Crane, 1957; Quitkin et al., 1979; Kline and

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Cooper, 1980; Hollister, 1981; Youdim, 1983]. These drugs, however, fell into disuse soon after their introduction, mainly because they were considered to be less effective than tricyclic antidepressant drugs (TCAs) [West and Dally, 1959; British Medical Research Council, 1965] and also because of the occurrence of hypertensive crises after exposure to food-contained tyramine [Horwitz et al., 1964; Blackwell, 1981; Dollery et al., 1984; Finberg and Youdim, 1984; Rabkin et al., 1985]. Thus MAO inhibitors (MAOIs) continued in limited use, with a claimed specificity of therapeutic benefit for "atypical depression" [West and Dally, 1959; Sargant and Dally, 1962; Klein and Davis, 1969], and patients with endogenous-type depression were considered to be poor responders to this class of drugs [Paykel, 1971; Robinson et al., 1978; Davidson et al., 1978]. In recent years, reversible MAOIs have been discovered and have attracted great interest, because the risk of hypertensive crisis appears to be less great with these compounds. The question remained, however, of whether the antidepressant efficacy of these novel MAOIs would be comparable to that of the TCAs.

Moclobemide belongs to this new class of reversible MAOIs [Keller et al., 1987] and has been shown, both in vitro and in vivo, to inhibit preferentially type A MAO [Da Prada et al.,, 1982, 1983, 1989]. The hypothesis according to which the risk of a hypertensive crisis should be less great with reversible MAOIs appears to hold true for moclobemide as judged from extensive studies performed in human volunteers examining the interactions of moclobemide with tyramine [see, e.g., Korn et al., 1988; Gieschke et al., 1988, Müller et al., 1988].

The purpose of this paper is to review the results of a clinical trial comparing moclobemide with clomipramine. The reason for chosing clomipramine as comparative drug was that it is well known in European psychiatry as a less sedating TCA (besides imipramine and desipramine).

METHODS AND PATIENTS

The principal objectives of the study were 1) to ensure that the efficacy of moclobemide given at a daily dose ranging from 300 to 600 mg/day is not inferior to that of clomipramine at a dose range of 75–150 mg/day and 2) to compare the tolerability and safety of moclobemide (300–600 mg/day) with those of clomipramine (75–150 mg/day).

Male and female outpatients 18–60 years of age were eligible for the trial. Patients were required to suffer from minor depression (DSM III). No minimum baseline total Hamilton score was specified, but tiredness was to be a predominant complaint.

Patients with schizophrenia, psychoorganic syndrome, or history of suicidal attempts were excluded, as were patients who abused drugs and alcohol, were suffering from severe organic illness (liver, kidney, blood), glaucoma, or prostatic hypertrophy or who had been treated with clomipramine or MAOIs in the 3 months prior to study entry. Pregnant females and those without safe contraception were also excluded.

The test dosage was flexible, 300–600 mg/day for moclobemide and 75–150 mg/day for clomipramine. Moclobemide in 100 mg tablets and clomipramine in 25 mg tablets were used. The initial dosage was three tablets daily, which could be increased up to a maximum of six tablets daily according to individual patients requirement.

The duration of the study was 6 weeks. During the treatment period, the concomitant use of other MAOIs was prohibited. In case of severe insomnia, a hypnotic could be given. It was recommended that consumption of tyramine-containing food be kept to a minimum or avoided. The patients were evaluated at weekly intervals.

Three main criteria were used to evaluate the efficacy. 1) The Hamilton Depression Rating Scale was used (HDRS; 24 items; for efficacy analysis, only the first 17 items were used). The final improvement (improvement at the individual treatment endpoint in percent of baseline) and time of first relevant improvement were calculated. (Time of the first reduction by 30% of the total score of the HDRS in the subset of those patients who showed a reduction at least twice during the treatment). 2) Investigator's overall assessment of efficacy was rated

according to the following scale: 1, very good; 2, good; 3, moderate; 4, poor. 3) We also used premature termination due to insufficient efficacy.

Other criteria were considered as secondary and will be discussed only descriptively: 1) the global impression on clinical status at treatment endpoint rated according to the following scale: 1, very good; 2, good; 3, moderate; 4, unchanged; 5, slight deterioration; 6, marked deterioration; 2) the investigator's assessment of onset and maximal effect; the day of onset of effect and the day of maximal effect were assessed by the investigator for patients in whom he found an antidepressant effect of treatment; 3) the concomitant therapeutic effects; for patients in whom therapeutic effects were found to be present, the investigator recorded the concomitant ones.

Safety and tolerability were evaluated by assessment of 1) vital functions (supine and standing blood pressure and heart rate, respiratory rate, the body weight); 2) laboratory examinations (hematology, blood chemistry, and urinalysis); side effects (all side effects observed by the medical staff or reported by the patient himself were recorded when judged by the investigator to be potentially drug related; side effects severity was scored on a four point scale as follows: 1, slight [patient is not bothered]; 2, moderate [patient is bothered]; 3, severe [requiring dose reduction or corrective treatment]; 4, very severe [requiring treatment withdrawal]; in addition, onset and duration of each side effect were recorded); 4) overall assessment of tolerance (at the end of treatment, the investigator rated the overall tolerability of the trial medication according to the following scale: 1, very good [no side effects]; 2, good [side effects, but no need for dose reduction or corrective therapy]; 3, moderate [side effects requiring dose reduction or corrective therapy]; 4, poor [side effects, treatment stopped]).

RESULTS

Demographic Data

Thirty-two patients were enrolled in the moclobemide treatment group: 10 male and 22 female, age range 26–76 years. Thirty-one patients were enrolled in the clomipramine treatment group: 14 male and 17 female, age range 24–76 years.

In five patients in the moclobemide group and in five patients in the clomipramine group, the limit of age (60 years) was exceeded. This was considered a minor protocol deviation.

Diagnosis of Depression

The two treatment groups were comparable concerning the status of the patient (inpatient, outpatient) and the mean duration of present depressive episode. Seventeen patients in the moclobemide and 15 in the clomipramine group suffered from endogenous depression (with one patient in the moclobemide and four in the clomipramine group suffering from a bipolar disorder). Eleven patients in each treatment group were diagnosed as suffering from a dysthymic disorder. The other diagnoses were (moclobemide group): neurotic depression (N = 1), reactive depression (N = 1), depression unspecified (N = 2); (clomipramine group): neurotic depression (N = 1), reactive depression (N = 1), major depression (N = 1), anxious depression (N = 2). It should be noted that the proportion of patients in whom depression was judged to be severe was higher in the clomipramine group (10 patients) than in the moclobemide group (six patients).

Other Related Treatments

During the wash-out period. Thirteen patients in each group were treated during the wash-out period. Twelve patients in each group received a benzodiazepine, and one in the moclobemide group was treated with a high-potency neuroleptic and one in the clomipramine group with lithium.

Concomitant somatic treatment. Fifteen patients in the moclobemide group and 13 in the clomipramine group underwent concomitant somatic treatment during the study.

Concomitant psychiatric treatment. Twenty-one patients in the moclobemide group and 19 in the clomipramine group underwent concomitant psychiatric treatment during the study: Many of them had more than one treatment. None of the three patients in the moclobemide group who were treated concomitantly with a neuroleptic was responder, whereas all the four patients in the clomipramine group were responders (as judged by the HDRS). One patient in the moclobemide group concomitantly received maprotiline, but the antidepressant effect was not greater than in the other patients.

Duration of Treatment

Five patients in the moclobemide group and ten in the clomipramine group were treated for less than 4 weeks. These patients were defined as prematurely withdrawn from the trial. Eleven patients in the moclobemide group and eight in the clomipramine group continued after 6 weeks. For efficacy evaluation, a duration of 4 weeks was used.

Dosage Regimen

The maximum mean total daily dosage was 450 mg/day on day 28 for moclobemide and 107.1 mg/day on day 21 for clomipramine.

Efficacy

1. The mean total Hamilton score (first 17 items) decreased in a similar fashion in both groups from baseline to day 28. Table 1 shows the decrease for the four HRDS-17 factors.
2. At the end of treatment, 43% of the patients in the moclobemide group and 38% in the clomipramine group had an improvement of more than 50% (Hamilton, first 17 items) compared with baseline. This difference was not significant (Wilcoxon-Mann-Whitney test).
3. In both groups, the first relevant improvement occurred within the first 3 weeks for 14 patients in the moclobemide group and 15 in the clomipramine group.
4. The investigator's overall assessment of efficacy is shown in Table 2. There was no significant difference between the treatment groups (Stucky-Vollmar test).
5. The lack of efficacy resulted in withdrawal of two patients in the clomipramine group but none in the moclobemide group.
6. The global impression on clinical status showed a rating of very good/good improvement in 11 patients (35.5%) in the moclobemide group and in 12 patients (41.4%) in the clomipramine group.
7. An antidepressant effect was stated as occurring in 15 patients in the moclobemide group and 17 in the clomipramine group. The onset of effect was comparable in both groups, but the maximal effect occurred later in the clomipramine group than in the moclobemide group.
8. The most often reported concomitant therapeutic effects were activating (moclobemide group, N = 7; clomipramine group; N = 9) and anxiolytic (moclobemide group; N = 5; clomipramine group, N = 4).

TABLE 1. Decreases in the (%) in the HRDS Factors

	Factor 1 (depression)	Factor 2 (agitation)	Factor 3 (anxiety)	Factor 4 (somatic complaints
Moclobemide	51	32	14	36
Clomipramine	51	57	37	38

TABLE 2. Investigator's Overall Assessment (%) of Efficacy

Assessment	Moclobemide	Clomipramine
Very good/good	46.4	54.1
Moderate/poor	53.5	45.8

Safety and Tolerability

1. The assessment of tolerance at treatment endpoint is shown in Table 3.

2. Side effects were reported in 20 (62.5%) patients in the moclobemide group and in 23 (74.2%) in the clomipramine group. Some patients had more than one side effect. Twenty patients in the moclobemide group reported 41 side effects and 23 patients in the clomipramine group reported 54 side effects). Table 4 shows the number and nature of side effects in the two groups.

3. In the moclobemide group, for 24 (of 41) side effects the duration was given, giving a mean of 7.3 days; for 26 side effects, the intensity was given a "severe/very severe" judgment in seven cases. In the clomipramine group, for 39 (of 54) side effects, the duration was given and the mean duration was 14 days. For 47 side effects, the severity of 22 was given a "severe/very severe" judgment. In three patients in the moclobemide group and seven patients in the clomipramine group, poor tolerability was mentioned (moclobemide group, agitation, tremor, tachycardia, dry mouth; clomipramine group, agitation, tremor, tachycardia, insomnia, hypotension, headache, nausea, vomiting, loss of appetite, dry mouth).

4. Vital functions were as follows. Blood pressure: values of mean systolic and diastolic blood pressures were slightly but not relevantly decreased in both groups. Considering the individual cases, there were two hypertensive and five hypotensive values in the clomipramine group and one hypotensive value in the moclobemide group. All changes were transient, and it was never necessary to terminate the trial in any patient for reasons of blood pressure changes. Heart rate: there were only slight variations of the mean heart rate in the moclobemide group; in the clomipramine group, the mean rate (standing) tended to increase. Body

TABLE 3. Investigator's Overall Assessment (%) of Tolerance

Assessment	Moclobemide	Clomipramine
Very good/good	71	51.6
Moderate/poor	29.1	48.4

TABLE 4. Number and Nature of Side Effects

	Moclobemide	Clomipramine
Dry mouth	5	6
Epigastric discomfort, nausea, vomiting, heart burn, constipation	6	7
Restlessness, tension, agitation	5	9
Hypotension	2	6
Tachycardia	6	2
Insomnia	2	6
Tremor, dyskinesia of extremities	3	6
Dizziness, headache, tiredness, itching hot flushes	4	4
Weight gain, taste sensation, anorexia	3	3
Trouble with potency, micturition disturbances	2	3
Others	3	2

weight: the mean body weight decreased slightly (1.5 kg) from baseline in both groups to day 28. Laboratory findings: generally, there was no evidence of clinically important drug-related changes of laboratory values, and none of the patients had to interrupt treatment because of abnormal values.

DISCUSSION

The patients enrolled in this study represent a heterogenous group, including endogenous-type depression and dysthymic disorder. The mean duration of the present episodes was 33.3 weeks (min 1 week, max 15 weeks) in the moclobemide group and 36.4 weeks (min 4 weeks, max 23 weeks) in the clomipramine group. In both groups, most of the patients had a marked depression. Ten patients in the clomipramine group and six patients in the moclobemide group were judged as having severe or very severe depression. Thirteen patients in each group were treated during the wash-out period (mostly with benzodiazepines). Many patients received concomitant somatic and psychiatric treatments. Twenty-one patients on moclobemide and 19 patients on clomipramine had concomitant psychiatric treatment (mainly with benzodiazepines), and many of the patients had more than one treatment.

The situation in this clinical trial is comparable to that in a psychiatrist's practice. Patients (mostly outpatients) with severe different forms and different severity of depression as well as with concomitant somatic diseases would be found there. It is usual that such patients would take benzodiazepines as well as undergoing other psychiatric and/or somatic treatment. Thus the situation in this study was similar to that in a real clinical condition; therefore, the results are of interest in that they give information which could be useful in the future, when the drug is on the market.

For the analysis, the results from the centers were pooled and analyzed according to the intent-to-treat principle. The results should be interpreted in light of the context. There were no significant differences between moclobemide and clomipramine with respect to all efficacy variables. The overall assessment of efficacy yielded 46.4% very good/good results for moclobemide and 54.1% for clomipramine. The final improvement in HRDS showed that 43% of the patients in the moclobemide group and 38% in the clomipramine group had an improvement of more than 50%. Two patients on clomipramine were withdrawn from the study, because of insufficient efficacy.

The investigator's global assessment of tolerability showed that tolerability was judged to be good or very good in 71% of patients on moclobemide and in 52% of patients on clomipramine. The number of side effects was greater in the clomipramine group than in the moclobemide group. The same also was true for severe or very severe side effects. Finally, three patients on moclobemide compared with seven on clomipramine were withdrawn from the study because of poor tolerability. Cardiovascular tolerability was satisfactory in both treatment groups. Concerning laboratory values, there was no evidence for clinically important drug-related changes. Thus, the comparison of moclobemide with clomipramine in this relatively unusual trial situation showed no relevant difference in efficacy. Tolerability was possibly superior in the moclobemide group.

REFERENCES

Blackwell, B.: Adverse effects of antidepressant drugs. 1. Monoamine oxidase inhibitors and tricyclics. Drugs **21**:201–219, 1981.

British Medical Research Council: Clinical trial of the treatment of depressive illness. Br. Med. J. **1**:881–886, 1965.

Crane, G.E.: Iproniazid (MARSILID) phosphate, a therapeutic agent for mental disorders and debilitating disease. Psychiatry Res. Rep. **8**:142–152, 1957.

Da Prada, M., Keller, H.H., Ketter, R., Schaffner, R., Pieri, M., Burkard, W.P., Korn, A., and Haefely, W.E.: Ro 11-1163, a specific and short-acting MAO inhibitor with antidepressant properties. In Kamijo, K., Usdin, E., and Nagatsu, T. (eds): "Monoamine Oxidase. Basic and Clinical Frontiers." Amsterdam: Excerpta Medica, 1982, pp. 183–196.

Davidson, J., McCleod, M.N., Blum, M.R.: Acetylation phenotype, platelet monoamine oxidase inhibitor and the effectiveness of phenelzine in depression. Am. J. Psychiatry **135**:467–469, 1978.

Dollery, C.T., Brown, M.J., Davies, D.S., and Strolin-Benedetti, M.: Pressor amines and monoamine oxidase inhibitors. In Tipton, K.F., Dostert, P., and Strolin-Benedetti, M. (eds.): "Monoamine Oxidase and Disease: Prospects for Therapy with Reversible Inhibitors." New York: Academic Press, 1984, pp. 429–441.

Finberg, J.P.M., and Youdim, M.B.H.: Reversible monoamine oxidase inhibitors and the cheese effect. In Tipton, K.F., Dostert, P., and Strolin-Benedetti, M. (eds.): "Monoamine Oxidase and Disease: Prospects for Therapy with Reversible Inhibitors." New York: Academic Press, 1984, pp. 479–486.

Gieschke, R., Schmid-Burgk, W., and Amrein R.: Interaction of moclobemide, a new reversible monoamine oxidase inhibitor with oral tyramine. In Youdim, M.B.H., Da Prada, M., and Amrein, R. (eds.): "The Cheese-Effect and New Reversible MAO-A Inhibitors." J. Neural Transmission [Suppl.] **26**:97–104, 1988.

Hollister, L.E.: Current antidepressant drugs. Their clinical use. Drugs **22**:129–152, 1981.

Horwitz, D., Lovenberg, W., Engelman, K., and Sjoerdsma, A.: Monoamine oxidase inhibitors, tyramine and cheese. J. Am. Med. Assoc. **188**:1108–1110, 1964.

Keller, H.H., Kettler, R., Keller, G., and Da Prada, M.: Short-acting novel MAO inhibitors: In vitro evidence for the reversibility of MAO inhibition by moclobemide and Ro 16-6491. Naunyn Schmiedebergs Arch. Pharmacol. **335**:12–20, 1987.

Klein, D.F., and Davis, J.M.: "Daignosis and Drug Treatment of Psychiatric Disorders." Baltimore: William and Wilkins, 1969.

Kline, N.S., and Cooper, T.B.: Monoamine oxidase inhibitors as antidepressants. In Hoffmeister, F., and Stille, G. (eds.): "Psychotropic Agents. Part 1. Antipsychotics and Antidepressants." Berlin: Springer, 1980, pp. 369–397.

Korn, A., Da Prada, M., Raffesberg, W., Allen, S., and Gasic, S.: Tyramine pressor effect in man: Studies with moclobemide, a novel, reversible monoamine oxidase inhibitor. In Youdim, M.B.H., Da Prada, M., and Amrein, R. (eds.): "The Cheese-Effect and New Reversible MAO-A Inhibitors." J. Neural Transmission [Suppl.] **26**:57–71, 1988.

Müller, T., Gieschke, R., and Ziegler, W.H.: Blood pressure response to tyramine-enriched meal before and during MAO-inhibition in man: Influence of dosage regimen. In Youdim, M.B.H., Da Prada, M., and Amrein, R. (eds.): "The Cheese-Effect and New Reversible MAO-A Inhibitors." J. Neural Transmission [Suppl.] **26**:105–114, 1988.

Paykel, E.S.: Classification of depressed patients: A cluster analysis derived grouping. Br. J. Psychiatry **188**:275–288, 1971.

Quitkin, F., Rifkin, A., and Klein, D.F.: Monoamine oxidase inhibitors: A review of antidepressant effectiveness. Arch. Gen. Psychiatry **36**:749–760, 1979.

Rabkin, J.G., Quitkin, F., Macgrath, P., Harrison, W., and Tricamo, E.: Adverse reaction to monoamine oxidase inhibitors. Part II. Treatment correlates and clinical managements. J. Clin. Psychopharmacol. **5**:2–31, 1985.

Robinson, D.S., Nies, A., Ravaris, C.L., Ives, J.O., and Bertlett, D.: Clinical psychopharmacology of phenelzine: MAO activity and clinical response. In Lipton, M.A., DiMascio, A., and Killam, K.F. (eds.): "Psychopharmacology: A Generation of Progress." New York: Raven Press, 1978, pp. 961–973.

Sargant, W., and Dally, R.: Treatment of anxiety states by antidepressant drugs. Br. Med. J. **1**:5–9, 1962.

West, E.D., and Dally, L.J.: Effects of iproniazid in depressive syndromes. Br. Med. J. **1**:1491–1494, 1959.

Youdim, M.B.H.: Implications of MAO-A and MAO-B inhibition for antidepressant therapy. Mod. Prob. Pharmacopsychiatry **19**:63–74, 1983.