A CONTROLLED DOUBLE-BLIND TRIAL OF MOCLOBEMIDE AND IMIPRAMINE IN THE TREATMENT OF DEPRESSION

L P Kok, W F Tsoi

ABSTRACT

The aim of this study is to compare the antidepressant efficacy and side effects of moclobemide with imipramine (a standard antidepressant). Moclobemide is a reversible inhibitor of monoamine-oxidase-A (RIMA) with selectivity for the MAO type A isoenzyme. Thirty-two patients who met DSM-3R criteria for major depressive episode or dysthymia were randomly assigned to receive either moclobemide or imipramine in a double-blind prospective study. The results indicated no difference in antidepressive efficacy between the two drugs, but imipramine had more anticholinergic side-effects. Neither drug had significant effects on pulse rate, blood pressure, weight changes or blood chemistry. These results were confirmed by previous studies.

Keywords: *antidepressant, imipramine, moclobemide, trial*

SINGAPORE MED J 1995; Vol 36: 38-40

INTRODUCTION

The aim of this study is to compare the antidepressant efficacy and side effects of moclobemide with imipramine (a standard antidepressant). Moclobemide, a benzamide derivative, is a reversible inhibitor of monoamine-oxidase-A (RIMA). It differs from the first generation monoamine-oxidase inhibitors (MAOI) like phenelzine and tranylcypromine by not having the so-called "cheese side-effect" ie hypertensive reactions to tyramine rich foods[1-3]. Moclobemide is not only reversible, it is also a specific inhibitor of monoamine-oxidase-A (MAO-A). The enzyme MAO exists in two forms designated A and B. MAO-A oxidises noradrenaline and serotonin and is related to symptoms of depression. Double-blind comparative clinical trials have shown that the efficacy of moclobemide was superior to placebo[4-9] and comparable to all the standard antidepressants: imipramine[5-7, 9-13], amitriptyline[8,14,15], clomipramine[9,16-18], maprotiline[19], fluvoxamine[20] and amineptine[21].

MATERIAL AND METHODS

Forty-four patients (psychiatric outpatients and inpatients at the National University Hospital) were enrolled in the study, of which 32 completed the trial and 12 dropped out. These 12 patients did not return for follow-up visits; 7 did not return after the first visit and the other 5 after the second visit. The reasons were not given. All subjects gave informed consent, fulfilled the DSM-3R criteria for major depressive episode or dysthymia and scored above 15 on the Hamilton Rating Scale for Depression. Exclusion criteria included: age above 70, recent ECT, high suicide risk, significant organic illness, including cardiac disorders, substance abuse or schizophrenia, and having taken antidepressant drugs within the past 5 days.

Patients were randomly allocated on a double-blind basis either to imipramine or moclobemide. Both medications were dispensed in identical capsules of 25 mg imipramine or 100 mg moclobemide (specially prepared) in bottles of 21 each. The dosage was fixed at imipramine 25 mg or moclobemide 100 mg to be taken at 8 am, 1 pm and 6 pm. Of the 32 patients who completed the trial, 15 were randomised to imipramine and 17 to moclobemide. There were no dietary restrictions. The patients were seen on day 0, day 7, and at the end of the trial on day 28 – the total length of the trial being 28 days.

At recruitment, a history was taken and a physical examination was carried out to confirm the diagnosis and to select the patients based on the inclusion and exclusion criteria. Before treatment, the patients were rated on the Clinical Global Impression Scale (Appendix 1), the Hamilton Rating Scale for Depression, and the Side-Effects Scale (Appendix 2). The pulse rate, blood pressure and weight were recorded. All the above measurements were repeated on the 7th day and 28th day of treatment. Blood was taken for alkaline phosphatase, alanine transaminase, aspartate transaminase, creatinine, gamma-glutamyl-transferase, glucose and urea, before treatment and on the 28th day. The study was approved by the hospital ethical committee, and was carried out under a certificate issued by the Medical Drug Trial Committee of the Ministry of Health, Singapore.

Appendix 1 – Clinical global impression (CGI)

1 = normal, not at all depressed
2 = borderline depressed
3 = mildly depressed
4 = moderately depressed
5 = markedly depressed
6 = severely depressed
7 = among the most extremely depressed patients

RESULTS

The sample consisted of 32 patients whose ages ranged from 20 to 68 years with the mean at 40.0 years. There were 14 males and 18 females. Seventy percent satisfied the DSM-3R criteria for major depression; and 30%, dysthymic disorder; 68% were

Department of Psychological Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

L P Kok, MD, DPM, FRCPsych, FRANZCP, FAMS
Associate Professor

W F Tsoi, MD, DPM, FRCPsych, FRANZCP, FRCPG
Associate Professor and Head

Correspondence to: Dr L P Kok
Kok & Tsoi Psychiatric Clinic
#10-08 Gleneagles Medical Clinic
6 Napier Road
Singapore 1025

Appendix 2 – Side-effects scale

Item	Symptoms	Range of Scores*			Scores
1	dry mouth	0	1	2	
2	constipation	0	1	2	
3	weakness	0	1	2	
4	giddiness	0	1	2	
5	drowsiness	0	1	2	
6	blurred vision	0	1	2	
7	nausea	0	1	2	
8	jitteriness	0	1	2	
9	others	0	1	2	

* 0 = nil, 1 = elicited, 2 = reported spontaneously.

Table I – Characteristics of sample

All cases	Imipramine 15 (47%)	Moclobemide 17 (53%)	Total 32 (100%)	
Age				
0-39	7 (22%)	6 (19%)	13 (41%)	NS
40-65	8 (25%)	11 (34%)	19 (59%)	
Mean	36.6 yrs	42.9 yrs	40.0 yrs	NS
S.D.	9.5 yrs	12.0 yrs	10.9 yrs	
Sex				
Male	6 (19%)	8 (25%)	14 (44%)	NS
Female	9 (28%)	9 (28%)	18 (56%)	
Severity				
Mild	4 (13%)	1 (3%)	5 (16%)	NS
Moderate	9 (28%)	13 (40%)	22 (18%)	
Severe	2 (6%)	3 (10%)	5 (16%)	
Illness duration				
0-30 days	3 (9%)	8 (25%)	11 (34%)	NS
31-90 days	7 (22%)	4 (12%)	11 (34%)	
91+ days	5 (16%)	5 (16%)	10 (32%)	

of moderate severity; 15 (47%) were allotted imipramine and 17 (53%) allotted moclobemide. There were no significant differences in the above variables between the imipramine and the moclobemide group (Table I).

All the cases showed improvement as indicated by reductions in the Clinical Global Impression scores between the first visit (day 0) and the second visit (day 7) ($t = 4.46$ $p = 0.000$), and between the first visit (day 0) and the last visit (day 28) ($t = 5.48$ $p = 0.000$); the improvements were confirmed by reduction in the Hamilton Rating Scale scores between the first visit (day 0) and the second visit (day 7) ($t = 8.85$ $p = 0.000$), and between the first visit (day 0) and last visit (day 28) ($t = 8.25$ $p = 0.000$). There were no statistically significant differences between imipramine and moclobemide in terms of antidepressant efficacy during these periods (Tables II and III). The imipramine group had higher overall scores for side-effects. The differences were significant on the 7th day (Table IV) and this was contributed by significantly higher scores for anticholinergic side-effects of dry mouth and constipation. There were no significant changes in blood pressure, pulse rate, weight and blood chemistry (alkaline phosphatase, alanine transaminase, aspartate transaminase, creatinine, gamma-glutamyl-transferase, glucose and urea), before and after treatment between the two groups. The imipramine subjects had a slight rise in mean pulse rate. The moclobemide group had slightly lower mean blood pressure on day 7, but this was contributed mainly by one case whose blood pressure dropped from 150/100 to 120/80. In all cases, the differences were not pathological.

Table II – Clinical global impression scores

Day of examination	Imipramine Mean	SD	Moclobemide Mean	SD	All cases Mean	SD	Sign. p value
Day 0	3.80	0.64	4.12	0.49	4.00	0.56	0.22
Day 7	3.33	0.90	3.23	0.83	3.28	0.86	0.75
Day 28	2.83	0.77	2.94	1.14	2.88	0.99	0.69
Day 7-0	0.53	0.83	0.88	0.99	0.72	0.92	0.29
Day 28-0	1.07	0.88	1.17	1.38	1.12	1.17	0.79

Table III - Hamilton rating scale scores

Day of examination	Imipramine Mean	SD	Moclobemide Mean	SD	All cases Mean	SD	Sign. p value
Day 0	17.67	4.29	19.12	4.66	18.44	4.49	0.36
Day 7	10.33	3.87	10.24	5.38	10.28	4.73	0.95
Day 28	8.20	3.59	8.35	5.01	8.28	4.41	0.92
Day 7-0	7.33	4.39	8.88	5.88	8.15	5.24	0.41
Day 28-0	9.47	6.44	10.76	7.55	10.16	7.05	0.61

Table IV – Side-effect scores

Day of examination	Imipramine Mean	SD	Moclobemide Mean	SD	All cases Mean	SD	Sign. p value
Day 0	1.67	2.29	1.59	2.06	1.63	2.17	0.92
Day 7	4.33	2.02	2.41	2.74	3.31	2.43	0.03*
Day 28	3.27	2.15	2.35	3.18	2.78	2.75	0.36
Day 7-0	2.67	3.06	0.82	2.32	1.69	2.69	0.06*
Day 28-0	1.60	2.92	0.76	2.22	1.16	2.57	0.37

* fairly significant

DISCUSSION

In this study, the two treatment groups were comparable in terms of age, sex and severity of depression. A marked antidepressant effect was found in both groups on both the 7th day and the 28th day of treatment, but there was no significant difference in antidepressant efficacy between moclobemide and imipramine. This is consistent with the many previous reports comparing moclobemide with tricyclic antidepressants[5-26]. The onset of action did not differ between imipramine and moclobemide, but Ucha Udabe et al[5] found a slight tendency to earlier response with moclobemide, and Casacchia and Rossi[12] found that moclobemide was superior to imipramine in the mean time of onset of effect. This was not confirmed in the present study. The response to treatment (in this study) with a drop of 7-9 points in the Hamilton scores of both the moclobemide and imipramine groups by day 7 could perhaps have been due to a placebo effect – Angst et al[21] in a meta analysis of 40 studies showed that milder cases of depression (less than 28 points on the Hamilton scale) had a greater placebo response. The majority (84%) of the patients in this study were not severely depressed, and would have probably been more likely therefore to have a greater placebo response. The drop of 7-9 mean points on the Hamilton

scale by day 7 was comparable to that found by Versiani et al[7] in a multicentre study of 490 patients using a 3 way trial (moclobemide, imipramine and placebo). By day 7, the Hamilton scores had fallen about 7 points in the 2 antidepressant groups and 6 points in the placebo group. A similar fall in Hamilton scores of about 7 points was also found in a Finnish study[22] of 6 outpatient clinics comparing moclobemide and imipramine in less severely depressed patients. Moclobemide had significantly less anticholinergic side-effects notably dryness of mouth, constipation, and drowsiness than imipramine. This has been confirmed by all studies comparing moclobemide with tricyclic antidepressants[5-26]. A New Zealand study comparing moclobemide to fluoxetine[27] showed that both were equally efficacious; in terms of adverse reaction fluoxetine resulted in more sedation, nausea and vomiting while those on moclobemide reported more insomnia. Unlike the traditional MAOIs, moclobemide does not have any serious effect on the patients' blood pressure. None of the cases showed a marked rise or fall in blood pressure. The slight mean increase in pulse rate (not significant compared to moclobemide) was likely to have been due to the adrenergic effects of imipramine – the increase in synaptic NA concentration. This finding was similar to the results of an analysis of clinical trials on 2,579 patients treated with moclobemide and a tricyclic antidepressant[23]. Biochemical tests for liver and renal functions and full blood counts were not affected by both drugs. Baumhackl et al[8] found that physical examination, body weight and laboratory values were essentially unaffected in both groups. In this study imipramine showed a slightly higher rise in mean pulse rate, and Versiani et al[7] also found an increase of the mean heart rate with imipramine, with the maximum at the end of week 1 when compared with moclobemide. There was no weight gain which is known to be associated with tricyclic antidepressants.

ACKNOWLEDGEMENTS

The authors thank Roche Singapore for sponsoring the study and supplying the drugs.

REFERENCES

1. Berlin I, Zimmer R, Cournot A, Payan C, Pedarriosse AM, Puech AJ. Determination and comparison of the pressor effect of tyramine during long-term moclobemide and tranylcypromine treatment in healthy volunteers. Clin Pharmacol Ther 1989; 46:344-51.
2. Zimmer R, Fischbach R, Breuel HP. Potentiation of the pressor effect of intravenously administered tyramine during moclobemide treatment. Acta Psychiatr Scand Suppl 1990; 360: 76-7.
3. Cusson JR, Goldenberg E, Larochelle P. Effect of a novel monoamine-oxidase inhibitor, moclobemide on the sensitivity to intravenous tyramine and norepinephrine in humans. J Clin Pharmacol 1991; 31:462-7.
4. Botte L, Gilles C, Evrard JL, Mesters P, Wolfrum C, Berger M, et al. Moclobemide versus placebo in the treatment of depression: a multicentre study in Belgium. Acta Psychiatr Scand Suppl 1990; 360:42-7.
5. Ucha Udabe R, Marquez CA, Traballi CA, Portes N. Double-blind comparison of moclobemide, imipramine and placebo in depressive patients. Acta Psychiatr Scand Suppl 1990; 360:54-6.
6. Versiani M, Nardi AE, Mundim FD, Alves A, Schmid-Burgk W. Moclobemide, imipramine and placebo in the treatment of major depression. Acta Psychiatr Scand Suppl 1990; 360:57-8.
7. Versiani M, Oggero U, Alterwain P, Capponi R, Dajas F, Heinze-Martin G, et al. A double-blind comparative trial of moclobemide v imipramine and placebo in major depressive episodes. Br J Psychiatry Suppl 1989; 6:72-7.
8. Baumhackl U, Biziere K, Fischbach R, Geretsegger C, Hebenstreit G, Radmayr E, et al. Efficacy and tolerability of moclobemide compared with imipramine in depressive disorder (DSM-III): an Austrian double-blind, multicentre study. Br J Psychiatry Suppl 1989; 6:78-83.
9. Biziere K, Berger M. Efficacy of a reversible monoamine oxidase-A inhibitor versus imipramine in subgroups of depressed patients. Acta Psychiatr Scand Suppl 1990; 360:59-60.
10. Casacchia M, Rossi A. A comparison of moclobemide and imipramine in treatment of depression. Pharmacopsychiatry 1989; 22:152-5.
11. Hebenstreit GF, Loidl M, Baumhackl U, Gallhofer B, Geretsegger C, Radmayr E, et al. Efficacy and safety of moclobemide compared with imipramine in the treatment of major depressive disorder. Double-blind multicenter study, Austria. J Neural Transm Suppl 1990; 32:77-84.
12. Bakish D, Bradwejn J, Nair N, McClure J, Remick R, Bulger L. A comparison of moclobemide, amitriptyline and placebo in depression: a Canadian multicentre study. Psychopharmacology (Berl) Suppl 1992; 106:98-101.
13. Beckers G, Vereecken A, de Bleeker E, Jaunes C, Sieben G, Faidherbe J, et al. Moclobemide versus amitriptyline in the treatment of depression: two small double-blind multicentre studies in Belgium. Acta Psychiatr Scand Supply 1990; 360:52-3.
14. Newburn GM, Fraser AR, Menkes DB, Mullen PE. A double blind trial of moclobemide versus amitriptyline in the treatment of depressive disorders. Aust NZ J Psychiatry 1990; 24:475-9.
15. Larsen JK, Holm P, Hoyer E, Mejlhede A, Mikkelsen PL, Olesen A, et al. Moclobemide and clomipramine in reactive depression. A placebo-controlled randomized clinical trial. Acta Psychiatr Scand 1989; 79:530-6.
16. Dierick M, Cattiez P, Franck G, Burton P, Defleur J, Hermans W, et al. Moclobemide versus clomipramine in the treatment of depression: a double-blind multicentre study in Belgium. Acta Psychiatr Scand Suppl 1990; 360:50-1.
17. Civeira J, Cervera S, Giner J, Allen SR, Hellstern K, Malanowski H, et al. Moclobemide versus clomipramine in the treatment of depression: a multicentre trial in Spain. Acta Psychiatr Scand Suppl 1990; 360:48-9.
18. Funke HJ, Moritz E, Hellstern K, Malanowski H. Moclobemide versus clomipramine in the treatment of depression: a single-centre study, Federal Republic of Germany. Acta Psychiatr Scand Supply 1990; 360:46-7.
19. Amrein R, Hitzel W, Stabl M, Schmid-Burgk. RIMA – A new concept in the treatment of depression with moclobemide. Int Clin Pharmacolog 1993; 7:123-32.
20. Silverstone T. Moclobemide – placebo – controlled trials. Int Clin Pharmacolog 1993; 7:133-6.
21. Angst J, Schneidegger P, Stabl M. Efficacy of moclobemide in different patient groups. Clin Neuropharmacol 1993; Vol 16 Suppl 2: S55-S62.
22. Rimon R, Jaaskelainen J, Kaartinen P, Kalli A, Kilponen R, Koskinen T, et al. Moclobemide versus imipramine in depressed outpatients: a double blind multicentre study. Int Clin Psychopharm 1993; 7:141-7.
23. Chen DT, Ruch R. Safety of moclobemide in clinical use. Clin Neuropharmacol 1993; 16 Suppl 2: S63-S68.
24. Laux G, Beckmann H, Classen W, Becker T. Moclobemide and maprotiline in the treatment of inpatients with major depressive disorder. J Neural Transm Suppl 1989; 28:45-52.
25. Bougerol T, Uchida C, Gachoud JP, Kohler M, Mikkelsen H. Efficacy and tolerability of moclobemide compared with fluvoxamine in depressive disorder (DSM III). A French/Swiss double-blind trial. Psychopharmacology (Berl) Suppl 1992; 106:102-8.
26. Macher JP, Mirabaud C. A double-blind comparison of moclobemide and amineptine in the treatment of depressed out-patients. Psychopharmacology (Berl) Suppl 1992; 106:116-7.
27. William R, Edwards RA, Newborn GM, Mullen R, Menkes DB, Segkar C. A double blind comparison of moclobemide and fluoxetine in the treatment of depressive disorders. Int Clin Jl Psychopharmacol 1993; 7:155-8.