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Mianserin and Lithium in the Prophylaxis of Depression

By ALEC COPPEN, KARABI GHOSE, RAMA RAO, JOHN BAILEY and MALCOLM PEET

SUMMARY **Forty-one out-patients with a history of at least three attacks of depressive illness were randomly allocated to treatment on a double-blind basis for one year with either mianserin 20 mg three times daily plus placebo lithium tablets, or to lithium tablets once daily plus placebo mianserin tablets. After one year, the dosage of mianserin was increased to 30 mg t.d.s. for a further six months. All but three of the patients had previously been stabilized on prophylactic lithium therapy. Lithium was found to be significantly superior to mianserin in avoiding admission to hospital or ECT. The overall affective morbidity index, calculated from global rating, showed no significant difference between drugs, but the index of the mianserin group was higher in the second six months than in the first. The lithium group showed no such change. Lithium remains the choice for the prophylaxis of unipolar recurrent depressive illness.**

Introduction

Lithium carbonate has been shown to be an effective prophylactic treatment for recurrent unipolar or bipolar affective illness (Coppen *et al*, 1973). Continuation treatment with tricyclic antidepressants for several months after an acute depressive episode appears to be successful in preventing relapse (Mindham *et al*, 1973; Paykel *et al*, 1976). However, there have so far been few studies in which antidepressant drugs were compared with lithium in long-term prophylaxis. In one study (Prien *et al*, 1973) imipramine was found to be as effective as lithium in recurrent unipolar, but not bipolar affective illness. In another study, maprotiline was found to be inferior to lithium (Coppen *et al*, 1976a).

Mianserin hydrochloride is a new tetracyclic antidepressant (Coppen *et al*, 1976b). In the present study, the prophylactic efficacy of mianserin was compared with that of lithium over an eighteenth-month period in patients with recurrent unipolar affective illness.

Methods

Patients who were receiving prophylactic lithium therapy were selected from the lithium clinic. Patients of either sex were included, with no age limits, and with unipolar affective illness manifested by at least three depressive episodes. The previous duration of lithium therapy and the apparent response or lack of response to previous lithium therapy, did not influence selection. Three patients had never previously received prophylactic lithium.

Patients with a history of other psychiatric or associated physical illness were excluded from the study as were pregnant or lactating women. Suitable patients were given an explanation of the nature of the trial and informed consent was obtained from them.

The patients were randomly assigned to

treatment with either mianserin plus placebo lithium or lithium plus placebo mianserin. Mianserin was given in a dose of 3 × 20 mg daily or the equivalent number of matching placebo tablets. After one year on the trial, patients receiving mianserin had their dosage increased to 90 mg daily for a further six months and the other group received an increased number of placebo tablets. Lithium tablets or matching placebo were given in a single daily dose, using the same number of tablets as the patient had previously been stabilized on. The dosage of lithium was adjusted to keep the plasma lithium level in the range 0.8–1.2 mol/l, adjustment being made by staff who were not involved in the assessment of patients. Placebo lithium dosages were changed with similar frequency in order to preserve blindness. Nitrazepam and daytime anxiolytics were allowed if essential and mild depressive episodes were managed with supportive psychotherapy. More serious depressive illness was treated by ECT, which was prescribed if necessary by the blind assessor. No other psychoactive medication was allowed. Patients were seen on average every six weeks or at shorter intervals during depressive episodes.

At each visit, clinical ratings were completed by a doctor who was unaware of the patient's medication. The degree of depression was rated on a 4-point scale, as follows:

3 severe depression

2 moderate depression

1 mild depression

0 no conspicuous affective disturbance

A side-effects checklist was also completed (Ghose, 1977). Each of 36 potential side-effects was rated on a 0–3 scale as absent, mild, moderate, or severe. Data were recorded on a specially designed chart, which is described elsewhere (Coppen *et al*, 1973). On this chart, it is possible to record graphically the depression ratings and also to record episodes of in-patient treatment, additional therapy and other parameters. In order to express the overall depressive morbidity of each patient, an affective morbidity index was calculated in the following way: a line was drawn between the points on the chart representing the scores on the morbidity ratings on each occasion; then the area under the curve was calculated and divided by the total time of study. Also used as measures of morbidity were the number of admissions to hospital with depressive illness, and the number of ECT courses. Blood was taken from all patients on each visit to the clinic before the morning dose of drugs. Plasma lithium levels (approximately 12 hours after the last dose of lithium) were measured on each visit. A sample of plasma was frozen and stored for subsequent estimation of mianserin levels (de Ridder, 1977).

Results

Details concerning the patients who entered the trial are shown in Table I. The patients in the lithium group showed significantly more affective morbidity ($P < 0.01$) over the year preceding the trial than did those in the mianserin group. Table II shows the details of patients who stopped the trial, with reasons in each case.

Affective morbidity index and side-effects

For the 28 patients who completed the first year of the trial, the scores on the affective morbidity index and side-effects checklist are shown in Table III. There are no significant differences between mianserin and lithium. The affective morbidity index in the mianserin group over the first year is higher than it had been over the year prior to the trial (Table I), but not significantly so. Data from the first, second and third six months of the trial period were compared for each treatment group. The affective morbidity index over the second six months of mianserin treatment (0.288 ± 0.09) is significantly ($P < 0.05$) higher than that during the first six months (0.162 ± 0.06), whereas that in the lithium group did not significantly alter between the two halves of the treatment period.

Relapses and other treatments

Details concerning the number of admissions to hospital and the extra treatment used are shown in Table IV. It can be seen that no patients in the lithium group required in-patient treatment or ECT, whereas seven

TABLE I

Characteristics of the patients who entered the trial

Treatment group	n	Sex		Age (yr)		Affective morbidity index during the preceding year	
		M	F	Mean	S.E.	Mean	S.E.
Lithium	20	10	10	54.6	2.2	0.17*	0.05
Mianserin	21	6	15	55.8	3.1	0.03	0.02

* Patients allocated to receive lithium had significantly higher affective morbidity index in previous year, excluding three patients who had not received lithium during that time.
Analysis of variance $P < 0.01$

TABLE II

Details of the patients who dropped out of the trial

Age	Sex	Time on trial (weeks)	Reasons for drop-out
			Mianserin group
61	F	0.1	*Side-effects: very sleepy and drowsy.
63	M	2	*Side-effects (unspecified).
55	F	2	*Side-effects: dizziness and diarrhoea.
71	M	3	*Wished to stop trial: no reason given.
55	F	12	*Not keeping well on new treatment.
54	F	14	Failed to re-attend the clinic.
51	F	24	*Wished to stop trial: no reasons given.
32	F	26	*Wished to stop trial and have open lithium.
			Lithium group
50	F	1.5	Diuretics to be prescribed.
73	F	2	*Felt depressed, shaking and giddy.
69	F	4	*Side-effects (unspecified). Irritable and unable to cope.
60	F	29	*Patient concerned about recurrent attacks of depression and migraine.
46	M	30	*Felt better. Discharged himself from the clinic.

* These patients stopped trial at their own request.

TABLE III

Affective Morbidity Index and side-effects score for patients who completed one year trial period

	Mianserin (60 mg daily)			Lithium		
	n	mean	S.E.M.	n	mean	S.E.M.
Affective morbidity index						
1st six months	13	0.162	0.06	15	0.201	0.05
2nd six months	13	0.288*	0.09	15	0.251	0.06
Total year	13	0.231	0.07	15	0.229	0.05
Side-effects score						
1st six months	13	7.00	1.48	14	8.17	1.45
2nd six months	13	7.39	1.37	14	8.62	1.84
Total year	13	7.20	1.33	14	8.42	1.62

* 2nd six months significantly greater than 1st six months.
Method of paired comparisons 't' = 2.355 $P < 0.05$

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TABLE IV

Number of in-patient episodes and amount of extra treatment needed for patients who completed one year of the trial

	Patients requiring admission		Patients requiring E.C.T.	
	One or more times	None	One or more courses	None
Mianserin	7*	6	5**	8
Lithium	0	15	0	15
Fisher exact probability	$P < 0.005$		$P < 0.025$	

* 4 with 1 admission
1 with 2 admissions
2 with 3 admissions

** 2 with 1 course
1 with 2 courses
2 with 3 courses

patients on mianserin required admission once or more and five patients required one or more courses of ECT. There was no significant difference between the two groups regarding the need for concomitant anxiolytic treatment.

Plasma concentrations of mianserin and therapeutic outcome

The mean plasma levels of mianserin found in this study were 36.7 ± 4.3, 38.9 ± 5.9 and 61.5 ± 11.6 ng/ml for the 1st, 2nd and 3rd six-month periods respectively. Similar mean plasma levels were found in our earlier investigation (Coppen *et al*, 1976b). There was a high correlation in plasma levels between the 1st, 2nd and 3rd six months periods, all correlation coefficients (r) being >0.89, $P < 0.001$. No correlation was found between plasma levels of mianserin and morbidity during the trial.

Discussion

In previous trials, mianserin has been shown to be effective in the treatment of acute depressive episodes for periods of up to six weeks (Coppen *et al*, 1976b; Murphy *et al*, 1976). The present study has shown that mianserin 60 mg or 90 mg daily is inferior to lithium as a prophylactic treatment for recurrent unipolar depression. In another study, we found that mianserin is ineffective in preventing bipolar affective illness and may even precipitate mania, in a way similar to other antidepressants (Coppen *et al*, 1977). Since almost all the patients were stabilized on lithium prior to the trial and were crossed over on to the trial medication, it might be argued that the patients are a pre-selected group. However, the practice in the clinic is to start all suitable patients on lithium and to encourage them to continue, regardless of the apparent level of response. The drop-out rate is less than 5 per cent per year. The bias of the trial was, if anything, against the lithium group, since by chance the level of morbidity over the year prior to the trial had been higher in the lithium group than in the mianserin group.

It could be suggested that there was an adverse effect due to withdrawal from lithium in the mianserin-treated patients. However, these patients showed more morbidity during the second six months of the trial than the first. This suggests that no withdrawal effect was present and also indicates that the effect of mianserin may be greater during the first six months of treatment than during the second.

No correlation was found between plasma levels and therapeutic effect of mianserin. A higher dosage of mianserin for a further six months did not suggest any additional therapeutic advantage over 60 mg daily. The data provide further evidence of the efficacy of lithium prophylaxis, in keeping with other reports (Coppen *et al*, 1973; Prien *et al*, 1973). In an earlier trial, mianserin was found to have a significantly lower total side-effects score than amitriptyline (Coppen *et al*, 1976b). In the present study, the mean total side-effects score did not differ significantly between mianserin and lithium.

Thus on the basis of available evidence, lithium remains the treatment of choice for the long-term prophylactic treatment of recurrent affective illness—both unipolar and bipolar.

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References

COPPEN, A., PEET, M., BAILEY, J., NOGUERA, R., BURNS, B., SWANI, M., MAGGS, R. & GARDNER, R. (1973) Double-blind and open studies of lithium prophylaxis in affective disorders. *Psychiatry, Neurology, Neurochirurgy*, **76**, 501-10.

—— MONTGOMERY, S. A., GUPTA, R. K. & BAILEY, J. (1976a) A double-blind comparison of lithium carbonate and maprotiline in the prophylaxis of the affective disorders. *British Journal of Psychiatry*, **128**, 479-85.

—— GUPTA, R., MONTGOMERY, S., GHOSE, K., BAILEY, J., BURNS, B. & DE RIDDER, J. J. (1976b) Mianserin hydrochloride—a novel antidepressant. *British Journal of Psychiatry*, **129**, 342-5.

—— GHOSE, K., RAMA RAO, V. A. & PEET, M. (1977) Mianserin in the prophylactic treatment of affective illness. *International Pharmacopsychiatry*, **12**, 95-9.

DE RIDDER, J. J. (1977) Advances in mass spectrometry. In *Biochemistry and Medicine* (ed A. Frigerio). Spectrum Publications, New York.

GHOSE, K. (1977) Lithium salts: therapeutic and unwanted effects. *British Journal of Hospital Medicine*, **18**, 578–83.

MINDHAM, R. H. S., HOWLAND, C. & SHEPHERD, M. (1973) An evaluation of continuation therapy with tricyclic antidepressants in depressive illness. *Psychological Medicine*, **3**, 5-17.

MURPHY, J. E., DONALD, J. F. & MOLLA, A. L. (1976) Mianserin in the treatment of depression in general practice. *Practitioner*, **217**, 135-8.

PAYKEL, E. S., DI MASCIO, A., KLERMAN, G. L., PRUSOFF, B. A. & WEISMANN, M. M. (1976) Maintenance therapy of depression. *Pharmacopsychiatry*, **9**, 127-36.

PRIEN, R. F., CAFEY, E. M. & KLETT, J. (1973) Prophylactic efficacy of lithium carbonate in manic-depressive illness. *Archives of General Psychiatry*, **28**, 337-41.

Alec Coppen, M.D., F.R.C.Psych., M.R.C.P., *Director*,

Karabi Ghose, Ph.D., M.R.C.P., *Senior Research Registrar*,

V. A. Rama Rao, D.M.P., M.R.C.Psych., *Senior Registrar*,

John Bailey, *Research Assistant*,
Medical Research Council Neuropsychiatry Laboratory, West Park Hospital, Epsom, KT19 8PB, Surrey

Malcolm Peet, D.P.M., M.R.C.Psych., *Medical Adviser, The Medical Unit, Organon Scientific Development Group, OSS, Holland*

Reprint requests to Dr A. Coppen.

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