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Further Report on Prophylactic Lithium in Recurrent Affective Disorders

By R. P. HULLIN, R. McDONALD and M. N. E. ALLSOPP

Introduction

Evidence continues to accumulate for the proposition that lithium salts have a marked prophylactic effect on recurrent affective disorders. An earlier paper (1), together with reports from Baastrup *et al.* (2) and Coppen *et al.* (3) indicate that this effect is a strong one. This paper reports the current position regarding a trial in one centre which has been in progress for eight years, in which the effect of lithium was investigated on the frequency of admission to and time spent in psychiatric hospitals.

Patients and Methods

The patients and methodology have been described previously (1). A comparison was made between a period in which a patient was receiving an appropriate dosage of lithium carbonate and the corresponding period immediately preceding the initiation of treatment. No patient in the trial had received lithium for less than 18 months, and all results were included even when in relapsed patients there was evidence of inadequate lithium or none in the blood plasma upon admission to hospital. The 95 patients involved include those considered in the previous study who were still receiving lithium, and also patients who have entered the trial since.

Results

The effect of prophylactic lithium treatment on the admission frequency and time spent in hospital related to age and sex is indicated in Table I. Although all groups show a very marked reduction in admission frequency and time spent in hospital when receiving lithium, it would appear that the improvement is most marked in males and least so in premenopausal females.

The results of lithium treatment with respect to sex and diagnostic category is considered in Table II.

Not surprisingly, in view of the anti-manic effect of lithium, unipolar manics of both sexes show a complete response to prophylactic lithium. It is of interest that there may be some sex difference between the response to lithium of unipolar depressives. No male patient in this category has been re-admitted during lithium

Table I

Effect of prophylactic lithium treatment on the admission frequency and time spent in hospital

Group	No.	Average age	Average time on lithium (months)	Average no. of admissions before treatment	Average no. of admissions during treatment	Average time in hospital before lithium treatment (weeks)	Average time in hospital during lithium treatment (weeks)
Pre-menopausal females	11	36	48	3·80	0·80	23·8	6·45
Post-menopausal females	47	60	53	5·11	0·63	38·7	5·50
Males	37	54	49	2·92	0·30	20·5	1·05
Whole group	95	66	50	4·11	0·71	29·7	3·91

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TABLE II

Complete lithium response related to age, sex and diagnostic category

Group	No.	Average age	Average time on lithium (months)	No. without re-admission (%)
Pre-menopausal females	11	36	48	5 (45)
Post-menopausal females	47	60	53	33 (70)
Males under 46	13	37	49	7 (54)
Males over 46	24	67	50	21 (87)
Unipolar manic: males	5	63	52	5 (100)
females	4	54	48	4 (100)
Unipolar depressives: males	11	51	40	11 (100)
females	25	54	51	18 (72)
Bipolar: males	20	53	52	11 (55)
females	27	57	52	15 (55)
Schizo-affectives (1 M, 2 F)	3	60	63	2 (67)

treatment, but 28 per cent of females have had at least one re-admission whilst receiving lithium. The bipolar group, irrespective of sex, do less well than those suffering from the unipolar form of illness. It should, however, be remembered that some of the relapses in this category were due to a failure to take the lithium tablets as directed. The data include 12 cases of this kind in which, upon admission, usually in mania, no lithium was present in the plasma.

SIDE EFFECTS AND ACUTE TOXICITY

(a) *Acute toxicity*

Since our last report we have had no further patients suffering from acute toxic effects, and almost all patients are without complaint of any obvious physical symptoms.

(b) *Thyroid function*

The evidence of a thyroid-depressing effect of lithium continues to grow, and we believe the case for some routine, regular assessment of thyroid function in lithium-treated patients is now very strong. Protein-bound iodide (PBI) levels, determined routinely, have been used as a screening procedure in this study. When persistently low values of PBI were found, further thyroid function tests such as triiodothyronine determinations and radio-active iodide uptakes have been performed. When these additional tests confirmed the presence of hypothyroidism, patients were placed on an appropriate dosage of thyroxine so as to restore the function test values to the euthyroid range. For 126 patients currently receiving prophylactic lithium in our trial (some of whom have not yet had 18 months of treatment and hence have been excluded from the above statistics) seven patients have given persistently low serial PBI values, and hypothyroidism has been confirmed by other thyroid function tests. The average time from commencement of lithium to the first low PBI value in this group was 54 months (range 30–75 months). In some of these patients during the early years of the trial lithium was discontinued, and within six weeks of discontinuation euthyroid values were re-established, though not without apparent psychiatric disadvantages. Latterly lithium treatment has been continued with thyroxine supplementation as described above. Of the 7 subjects who became hypothyroid, 4 (1 male, 3 females) had high titres of thyroid antibodies, which antedated the reduced thyroid function. However, two other female patients who have been receiving prophylactic lithium for periods of 43 and 72 months respectively, have not yet shown low PBI values despite having high titres of thyroid antibodies.

In addition to these 7 patients, another 4 (2 male, 2 female) have shown low PBI values on at least five occasions, but the results of other thyroid function tests have been equivocal. No change in medication has therefore been insti-

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tuted, but these patients are seen at more frequent intervals and their thyroid status is closely monitored. Transient low PBI values have also been found in 16 other patients receiving prophylactic lithium.

Thus, to summarize, 5·6 per cent of the patients have developed persistent hypothyroidism, another 3·2 per cent have given low PBI values on more than five occasions and a further 12·7 per cent have shown occasional low values for PBI. Hence, in total, 21·5 per cent of patients in the trial have shown some indication, albeit only occasionally, of reduced thyroid function. Since many of the early clinical symptoms of hypothyroidism are difficult to distinguish from those of depression, there is a strong case for including some screening test of thyroid function in all patients receiving prophylactic lithium.

(c) *Calcium metabolism*

It has been shown that lithium is retained in bone (4), and that although one fraction of the retained lithium is labile and disappears within 4 to 5 days of discontinuing lithium treatment there is a second fraction (approximately 50 per cent) which is tenaciously retained and does not disappear from bone for periods of many weeks or months (5). This finding, obtained in rats receiving lithium in their drinking water, has been confirmed in human post-mortem tissue obtained in three cases in which lithium had been stopped for periods varying from three to nine months before death. It is probable that the retention of lithium in bone and its subsequent release due to resorption provides an explanation of our finding in metabolic balance studies (6) that after discontinuation of lithium treatment discrete periods of 2 to 5 days occur when the cation reappears in both plasma and urine. We have been carrying out studies in conjunction with the M.R.C. Mineral Metabolism Unit, Leeds, to determine whether the lithium retained in bone or the effect that lithium has on calcium metabolism by virtue of its diagonal relationship in the Periodic Table has any adverse consequences on the bone metabolism of patients receiving lithium for very long periods. The results of these investigations will be presented in due course.

Discussion

Assuming that the natural history of recurrent affective disorders is not characterized by decreasing episode frequency with increasing age —and there is evidence suggesting this is not so (7), this further report provides more evidence that lithium exerts a strong prophylactic effect against this illness. The problems of categorizing those patients likely to respond to treatment and of determining which biological action of lithium is responsible for its beneficial psychiatric effect now assume considerable importance both clinically and in clarifying the aetiology of recurrent affective disorders.

Appropriate preliminary screening of patients and regular monitoring of plasma lithium levels have minimized the possibility of acute toxic effects. The occurrence of long-term lithium effects on thyroid and calcium metabolism requires careful assessment and consideration in preliminary screening procedures and in routine monitoring.

Summary

A further report on the effect of lithium as a prophylactic agent against recurrent affective disorder is presented. A group of 95 patients was studied for an average period of 50 months (range 18–96 months). The number of admissions to and time spent in a psychiatric hospital during lithium treatment were compared in each patient with the situation in an equivalent period immediately prior to the commencement of prophylactic treatment. The average number of admissions for episodes of depression and/or mania fell from 4·11 to 0·71 and the average time spent in hospital from 29·7 to 3·9 weeks. Sixty-six of the patients in the group have not been readmitted to hospital while receiving lithium; these total responders included the whole of the 9 unipolar manics and 11 unipolar male depressives. Patients with bipolar manic-depressive psychosis had the lowest percentage (55 per cent) of total responders.

The occurrence of long-term side-effects of lithium on thyroid function and calcium metabolism is discussed.

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