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Lithium in Non-Manic-Depressives: Antiaggressive Effect and Red Blood Cell Lithium Values

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Summary

Lithium was given to eight aggressive, non-manic-depressive female defectives in a double-blind placebo-controlled study. The group as a whole showed a reduction in aggression scores while on lithium ($p < 0{\cdot}01$): three patients became less aggressive, one became worse and two were unchanged. Both affective and predatory aggression seemed to be reduced. Two patients had to be withdrawn from the trial at an early stage because of the development of neurotoxicity.

R.B.C./plasma lithium ratios showed a wide inter-patient variation in this group of non-manic-depressives.

The study adds further weight to evidence that lithium has an antiaggressive effect at normal therapeutic dosage in non-manic-depressives. The implications of this for hypotheses about the mode of action of lithium and its putative specificity for manic-depressive psychosis are discussed.

Introduction

Lithium carbonate is now an established drug in British psychiatric practice, and it is accepted that the primary indication for the use of the drug is in manic-depressive psychosis. However, some investigators have suggested that this drug may have useful effects in other conditions. In particular, it has been claimed that lithium has an antiaggressive effect (Sheard, 1970, 1971 and 1973; Weischer, 1969; Tupin *et al.*, 1973; Dostal, 1971; and Morrison *et al.*, 1973).

The present study was an attempt to assess the antiaggressive effect of lithium in aggressive severely subnormal female patients. The drug was given on a double-blind basis, and as part of the routine lithium estimations we measured red blood cell lithium levels.

Subjects

The subjects were 8 severely subnormal female patients in one ward of a mental deficiency hospital. Two suffered from phenylketonuria, one was a mongol, one was thought to be defective following encephalitis at age 2 years and in the remaining four the cause of the mental deficiency was unknown. In age they ranged from 33 to 57 years. All had shown frequent aggressive behaviour for many years: seven patients regularly struck, bit, nipped or scratched other patients with or without obvious provocation, and one patient severely scratched her own face and damaged property when frustrated. None of the eight was considered to show clinical evidence of manic-depressive psychosis using the criteria of Reid (1972), though one patient had a family history of manic-depressive psychosis—a brother having been admitted on several occasions to a psychiatric hospital with mania and depression (Patient No. 3, Table I).

Method

Nursing staff, who were blind to the medication being given, rated aggressive behaviour as follows. Each nurse in contact with any of the patients during one or more of three blocks of time each day: 8 a.m.–12 noon; 12 noon–5 p.m.; 5 p.m.–9 p.m.—rated aggressive behaviour on a simple 7-point scale for the appropriate intervals. Prior to the start of the trial this rating

TABLE I

Patient	Age (years)	Mental deficiency diagnosis	Lithium levels during the last 3 weeks of each lithium administration mEq./l.		Effect of lithium on aggression scores	Probability χ^2 test
			Mean plasma	Mean R.B.C.		
1	54	Idiopathic mental deficiency	0·87	0·43	Unchanged	$p < 0·5$ N.S.
2	42	Phenylketonuria	0·76	0·30	Improved	$p < 0·001$ H.S.
3	35	Phenylketonuria	0·93	0·33	Worse	$p < 0·001$ H.S.
4	39	? Post-encephalitic brain damage	0·87	0·59	Improved	$p < 0·05$ Probably sig.
5	44	Idiopathic mental deficiency	0·74	0·46	Unchanged	$p < 0·8$ N.S.
6	57	Epiloia	1·38	0·82	Withdrawn from trial	
7	51	Mongolism	1·16	0·50	Withdrawn from trial	
8	33	Idiopathic mental deficiency	0·77	0·69	Improved	$p < 0·001$ H.S.

scale had been shown to have high inter-rater reliability. A final aggression score for each patient during each of the three daily blocks of time was calculated using the median score of the ratings for that time, i.e. each patient ended up with three median ratings of aggression per day for the length of the trial.

Each patient was given lithium or placebo alternately for intervals of four weeks during the 16-week investigation period. Seven of the patients were initially randomly assigned to commence lithium or placebo. Two of the patients had to be withdrawn from the trial because of severe toxic effects during the first period of lithium administration (patients 6 and 7, Table I), and patient No. 8 (Table I) was added late to the trial and only received placebo for four weeks followed by lithium for four weeks. Each patient received five trial tablets per day: during the lithium periods this consisted of trial Priadel (400 mg.) tablets to the dosage required and added placebo tablets to make up the five tablets. Dosage of lithium was adjusted at the end of each week to produce plasma lithium levels in the range 0·6–1·4 m.Eq./l. at 16–24 hours after the last lithium dose.

Psychotropic medication being prescribed for the patients before the start of the trial was continued unchanged throughout the trial.

Venous blood samples were taken from each patient twice weekly during the first eight weeks of the trial and weekly thereafter. Plasma lithium estimations were made on each of these samples, whether the patients were being prescribed lithium or placebo, and the R.B.C. lithium estimations were made once weekly from these blood samples. On only one occasion did the plasma lithium level not concur with the prescribed medication: a patient who was supposedly receiving placebo had a plasma lithium level of 0·11 m.Eq./l. This level would be consistent with a single drug administration error the previous day.

Red cell lithium was estimated as follows: 10 Ml. heparinized blood specimens were centrifuged at 1,500 g. for one hour. 2 Ml. of plasma was

withdrawn for lithium analysis and the remaining plasma and top 5 mm. of red cells were aspirated. The cells were vortexed and duplicate 0·5 ml. aliquots were thoroughly mixed with 9·5 ml. deionized water. (Blood pipettes were washed out thoroughly with diluent until all traces of red cells adhering to the sides had disappeared.) The lithium content of these solutions were determined by atomic absorption spectrophotometry against suitable standards.

Plasma lithium was determined by the method of Pybus and Bowers (1970).

Results

The first weeks of lithium and placebo administration were regarded as build up and washout phases respectively and ignored in the initial comparison. Considering the group as a whole, the periods on lithium and placebo were compared by means of a 4×2 Chi square table. This table considered aggression scores 1–1·9; 2–2·9; 3–3·9; and 4–7, representing no aggression, moderate degrees of aggression and marked degrees of aggressive behaviour. There was significantly less aggression shown during periods on lithium ($p < 0·01$) (Table II). However, this group result masked wide individual variations. Comparing lithium and placebo periods for each patient by means of the same 4×2 Chi square table showed that three patients became less aggressive on lithium; two of the results were highly significant ($p < 0·001$) and one was probably significant ($p < 0·05$). One patient became significantly more aggressive on lithium ($p < 0·001$) and two were unchanged (Table I). The patient who became worse showed an increase in moderate degrees of aggressive behaviour (median scores 3–3·9) but not in more marked degrees of aggression. Paradoxically, she was the only one with a family history of manic-depressive disorder.

Table II

Grouped aggression scores for all 6 patients completing the trial

	Aggression scores			
	1–1·9	2–2·9	3–3·9	4–7·0
Pl. ..	328	128	99	135
Li. ..	378	130	90	92

$\chi^2 = 12·2$; $P < 0·01$

Fig. 1 illustrates the response pattern of patient No. 2 and shows the mean weekly aggression scores over the 16 weeks of the trial.

Graphing the mean daily aggression scores of the two clear-cut responders against time showed that a demonstrable response occurred by the second week of lithium administration.

The usual pattern of aggressive behaviour in the three who responded to lithium was as follows. Patient No. 2 (Table I) struck and pushed other patients in retaliation and struck other patients and nursing staff when closely confined with others in a cramped space, e.g. 'the

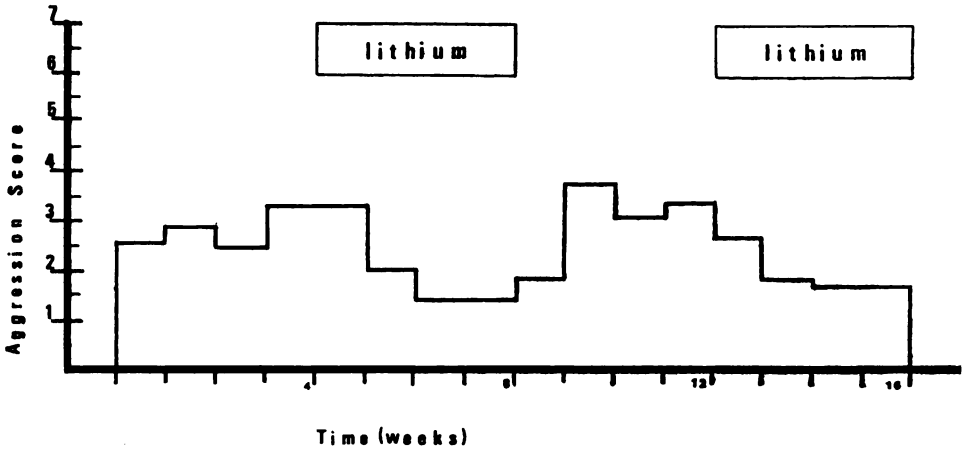

Fig. 1.—Patient No. 2. Mean weekly aggression scores.

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face room'. Patient No. 4 was the patient with temper tantrums described earlier; her aggression was always directed at herself or property. Patient No. 8 attacked other patients without obvious provocation. The nursing staff regarded her as being sadistic. Thus two appeared to show affective aggression and one, No. 8, predatory aggression.

R.B.C. lithium : plasma lithium ratios showed a wide patient to patient variation from the lowest at 36 per cent to the highest at 90 per cent and appeared unrelated to the clinical response.

Patients No. 6 and 7 had to be withdrawn from the trial because of serious signs of neurotoxicity during the third week of the first period of lithium administration. The maximum plasma levels occurring in these two patients were 1·49 m.Eq./l. and 1·23 m.Eq./l. respectively. Patient No. 6 had evidence of cerebrovascular disease before the start of the trial and died of a clinically diagnosed cerebrovascular accident 19 days after being withdrawn from the trial (post-mortem permission was refused). Patient No. 7 had been considered to be showing signs of a progressive dementia. The clinical signs of neurotoxicity common to both included truncal ataxia, marked anorexia without vomiting, and a severe degree of aspontaneity without drowsiness and with insomnia* at night.

Discussion

Sheard (1970; 1973) showed that lithium in rats inhibited foot-shock-induced aggression and virtually abolished territorial aggressive behaviour. Weischer (1969) reduced aggression in Siamese fighting fish with lithium. Tupin *et al.* (1973) reported an open trial of lithium in aggressive prisoners with a variety of diagnoses but excluding manic-depressive disorder: Fourteen out of his 27 subjects were noted to be substantially less aggressive on lithium. Dostal (1971), in an open trial of lithium in 14 aggressive mentally defective adolescent boys, reported that the group as a whole showed reduced aggression while on the drug. Morrison *et al.* (1973), in what appears to have been a single blind study, gave placebo for three weeks followed by lithium for three weeks to seven 'hyperaggressive' patients—three schizophrenics and four personality disordered patients. Two out of these seven showed a more than 25 per cent decrease in aggression-hostility ratings on five selected items from a 21-item nurse rating schedule. Sheard (1971) in the most rigorous study reported to date, gave lithium alternating with placebo for four-week periods to 12 aggressive, non psychotic inmates of a maximum security prison. This study was designed to be single blind. He found a significant reduction in self-rated hostility for the group as a whole. More importantly, it was found that the prison staff, who were blind to the medication being given, administered fewer 'tickets' for physical or verbal aggression to the group during lithium periods.

The study reported here adds further confirmatory evidence to the claim that lithium has antiaggressive properties at normal therapeutic dosage in non-manic-depressives.

The clinical response in the two patients showing a highly significant response (a total of three treatment periods) was clearly detectable by the second week of lithium administration. This period resembles that found in treating manics with lithium (Schou, 1968; Johnson *et al.*, 1968; and Prien *et al.*, 1972).

Because of the high response rate in the acute treatment of mania and in the longer term treatment of recurrent mania and psychotic depression compared to the very variable response in other psychoses and behaviour disorders suggestions have been made that lithium is a disease-specific treatment (e.g. Schou, 1963; Johnson *et al.*, 1968), and this view is now widely held. Hypotheses about the biochemical abnormalities in manic-depressive psychosis and the mode of action of lithium have been made based on this assumption (e.g. Mendels and Frazer, 1973; Glen and Reading, 1973). However, the response of episodes of manic-depressive disorder to a large variety of potent agents—tricyclic antidepressants, phenothiazines, butyrophenones and ECT—considered alongside demonstrations of a change in behaviour at normal therapeutic lithium levels in non-manic-depressives suggests that it is not so much the lithium treatment that is specific but rather that

* Eight out of Sheard's 12 non-manic-depressive patients reported sleeplessness while on lithium (Sheard, 1971).

it is manic-depressive disorder that is unique. Whilst in clinical practice manic-depressive psychosis is the primary indication for the use of lithium, hypotheses about the mode of action of lithium in this condition should take into account its more widespread psychopharmacological actions.

The occurrence of serious signs of neurotoxicity, at plasma lithium levels not inordinately high, in two of these patients—the two suspected of having *progressive* brain damage—re-emphasizes that caution is required in treating brain-damaged patients with lithium. Similar signs of neurotoxicity have been described in other brain-damaged patients at plasma lithium levels within the customarily accepted therapeutic range (Shopsin and Gershon, 1973).

It has been claimed that R.B.C. lithium : plasma lithium ratios may distinguish unipolar from bipolar depressions (Elizur *et al.*, 1972) and may indicate which depressed patients will respond to lithium (Mendels and Frazer, 1973), and that high R.B.C. lithium values may be a better index of toxicity than plasma levels (Elizur *et al.*, 1972). The wide variation in R.B.C. lithium : plasma lithium ratios in the present group of non-manic-depressive patients is noteworthy. In the two patients who had to be withdrawn from the trial there was no indication that the absolute R.B.C. lithium level was a better guide to impending neurotoxicity than the plasma lithium level (see Table I).

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