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Lithium Side Effects in a Routine Lithium Clinic

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SUMMARY Approximately two thirds of a group of bipolar patients attending the routine lithium clinic suffered side effects. These patients tended to have a lower plasma and erythrocyte lithium concentration and a lower erythrocyte/plasma lithium ratio than those who had no side effects. Explanations of this unexpected finding are discussed.

Introduction

Lithium is now established as a useful drug in the prevention of recurrence of manic-depressive psychosis. However, minor but unpleasant side effects occur and may lead patients to reject treatment. It is uncertain how common such side effects are; the data sheet of 'Priadel', for instance, states that 'transient side effects may occur during stabilization but are unlikely to do so at serum lithium levels below 2 mEq/l'; that of 'Phasal' states that 'side effects are usually related to blood lithium levels and are infrequent at levels below 1.5 mEq/l'. In contrast, Hewick *et al* (1977) have reported minor side effects in over 40 per cent of patients stabilized on long-term lithium therapy.

It has also been suggested that side effects are related more closely to intracellular levels of lithium than to plasma levels (Elizur *et al*, 1972; Zakowska-Dabrowska and Rybakowski, 1973). The concentration of lithium in erythrocytes has been shown to correlate more closely than plasma levels with brain levels of lithium (Frazer *et al*, 1973). Erythrocyte lithium concentration has therefore been suggested as a more useful routine assay than plasma lithium (Frazer *et al*, 1973; Dorus *et al*, 1975). The ratio of lithium concentration in the erythrocyte to that in the plasma varies from individual to individual but has been claimed to be relatively stable within an individual and even claimed to be genetically determined (Dorus *et al*, 1975). Though the main controversy has surrounded the use of this ratio in predicting therapeutic response, it has also been suggested that the ratio is related to side effects, i.e. those with a high ratio would have a high intra-erythrocyte (and therefore intracellular) lithium level and therefore be more prone to side effects (Elizur *et al*, 1972). However, Lee *et al* (1975) have criticized the use of this ratio, showing that it is not stable but changes with change in plasma lithium concentration. *In vitro* studies (Ratey and Mallinger, 1977) tend to confirm the dependence of the ratio on plasma concentration.

Lithium probably affects transport across membranes (Peet, 1975) and has been reported to affect erythrocyte Na-K ATPase (Naylor *et al*, 1974; Hesketh, 1976). The main interest has been whether such changes are related to the therapeutic effectiveness of lithium, but it is not known whether this is related to side effects. The present study attempts to explore the relationship of side effects of lithium, in patients who were stabilized on the drug, to measures of sodium pump activity, to plasma and erythrocyte lithium levels and to the particular preparation of lithium used.

Method

Forty-nine bipolar manic-depressive patients attending the routine lithium clinic of the Dundee Psychiatric Service were investigated. Venous blood was taken from the patient between 9 and 10.30 a.m. on two separate visits to the clinic. On each of these two visits, as on all routine visits to the clinic, the patients were questioned about side effects and were examined for the presence of tremor. The severity of side effects was rated on a simple scale 0—absent, 1—mild, 2—moderate, 3—severe. All patients had been stabilized on lithium for at least

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several months, and blood samples were taken not less than 10 hours after the last dose of lithium.

The plasma sodium, potassium and lithium concentrations were determined, using an atomic absorption spectrophotometer and appropriate standards. Erythrocyte sodium, potassium and lithium concentrations were determined by a modification of the washing method of Smith and Samuel (1970), using tris buffered choline chloride instead of magnesium chloride as the washing solution. Erythrocyte Na-K ATPase was estimated in washed erythrocyte ghosts by the ouabain-sensitive release of inorganic phosphate from ATP (Bonting, 1970).

Results

The 49 patients investigated included 16 men (mean age 48, s.d. 13 years) and 33 women (mean age 48, s.d. 11 years). The stability of most of the parameters is shown by the strong positive correlation between the estimations on the two occasions (Table I). On a few patients we have only one estimation of some of the biochemical parameters.

There were, of course, slight changes between the two estimations. The changes in plasma lithium between the two occasions correlated positively with the change in the erythrocyte/plasma lithium ratio ($N = 38$, $R = +0.349$, $P < 0.05$). Similarly, the changes in erythrocyte lithium concentration correlated significantly with the change in the ratio ($N = 38$, $R = +0.750$, $P < 0.001$).

There was a strong positive correlation between the erythrocyte lithium concentration and the plasma lithium concentration (first assay $N = 44$, $R = +0.759$, $P < 0.001$, second assay, $N = 47$, $R = +0.662$, $P < 0.001$).

Unexpectedly, the side effects reported were the same on each of the two visits, and their frequency is shown in Table II. Of the 49 patients only 18 were free from side effects. The most common side effects were tremor or the thirst–polydipsia–polyuria syndrome. Tremor was more common in males, polyuria in females, but neither difference was statistically significant using the χ^2 test with Yates' correction ($P > 0.05$).

To relate side effects to blood results, patients were initially divided into two groups, those who had any side effects and those who had none. For each individual the mean of two biochemical estimations was used in the calculation (except where only one estimation available). Since total side effects were equally common in men and women, the results of the two groups were simply compared by a t test for uncorrelated means (Table III).

There was no significant difference in erythrocyte Na-K ATPase, sodium or potassium concentration or plasma sodium or potassium concentration between those who were suffering

TABLE I

Correlation between the estimations on two occasions

	N	r	P
Plasma lithium	39	+0.488	<0.005
Erythrocyte lithium	39	+0.480	<0.005
Erythrocyte plasma-lithium ratio	38	+0.636	<0.001
Erythrocyte sodium concentration	47	+0.702	<0.001
Erythrocyte Na-K ATPase	48	+0.482	<0.005

TABLE II

Number (and %) of side effects encountered

	N	Tremor	Thirst/Polyuria	Gastrointestinal side effects	Hypothyroidism	Other
Male	16	8 (50)	4 (25)	2 (12.5)	2 (12.5)	1 (6.25)
Female	33	7 (21)	18 (55)	3 (9)	2 (6)	2 (6)

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TABLE III

Biochemical parameters in patients with and without side effects

		Erythrocyte				Plasma			
		Na-K ATPase †	Na mmol/l	K mmol/l	Li mmol/l	Na mmol/l	K mmol/l	Li mmol/l	Ratio of erythrocyte plasma lithium concentration
Patients with side effects	N	31	31	31	31	29	31	31	31
	Mean	1.70	7.31	99.6	0.394	138	4.26	0.787	0.500
	s.e.m.	0.05	0.22	0.6	0.029	1.0	0.08	0.036	0.025
Patients without side effects	N	17	17	17	17	16	17	17	17
	Mean	1.75	7.05	100.0	0.560	139	4.39	0.930	0.617
	s.e.m.	0.08	0.22	1.0	0.045	1.0	0.10	0.056	0.052
P		NS*	NS*	NS*	<0.001	NS*	NS*	<0.05	<0.05

† mmol PO_4/l, RBC, h.
* P >0.05.

TABLE IV

Characteristics of patients with and without side effects

	N	Male	Female	Drug taken: Camcolit	Priadel	Other	Dose (mg/day) Mean ±s.e.m.	Age (years) Mean ±s.e.m.
Patients with side effects	31	10 (32%)	21 (68%)	15 (48%)	14 (45%)	2 (7%)	1166 ±65	49 ±2
Patients without side effects	18	6 (33%)	12 (67%)	7 (39%)	8 (44%)	3 (17%)	1122 ±96	47 ±3
P		NS*			NS*		NS*	NS*

* P >0.05

side effects and those who were not. However, patients who were suffering from side effects had significantly lower plasma and erythrocyte concentrations of lithium and had significantly lower erythrocyte/plasma lithium ratios. There was no significant difference between the two groups in the mean dose of lithium prescribed (Table IV). Similarly there was no significant difference between the ratio of plasma lithium to dose prescribed between the two groups. Side effects were as frequent in patients on Priadel as in patients on Camcolit.

The two most common side effects (tremor and polyuria) were examined separately, but because of possible unequal sex distribution data from men and women were analysed separately (e.g. men with tremor compared with men without tremor, men with polyuria compared with men without polyuria, etc.). The only statistically significant results to emerge from this analysis were that women with thirst and polyuria had significantly lower erythrocyte lithium concentrations and lower plasma potassium concentrations than women without thirst and polyuria.

Plasma and erythrocyte concentrations produced by Priadel and Camcolit are shown in Table V. In both men and women the dose of Priadel prescribed was slightly but not significantly higher than that of Camcolit. The plasma level in women on Priadel was significantly lower (P <0.05) than that of women on Camcolit; the erythrocyte concentrations were also lower, but the difference did not

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TABLE V

Plasma and erythrocyte concentrations of lithium in patients on Camcolit and Priadel

		Dose (mg)		Plasma concentration (mmol/l)		Erythrocyte concentration (mmol/l)	
	N	M	SD	M	SD	M	SD
Males							
Camcolit	4	1187	375	0.85	0.17	0.55	0.22
Priadel	12	1225	431	0.93	0.24	0.45	0.20
Females							
Camcolit	18	1083	363	0.85	0.14	0.46	0.14
Priadel	10	1320	342	0.68	0.22	0.34	0.14

reach statistical significance ($0.05 < P < 0.1$). There was no significant difference between the plasma or erythrocyte levels with the two preparations in the men. Five patients were receiving other lithium preparations (3 as Phasal, 2 in liquid form).

Discussion

The most striking feature of the study was the high incidence of unwanted side effects even though patients had been on the drug for long periods. Approximately two thirds of the patients suffered from side effects. This is in striking contrast to statements in the data sheets of the manufacturers. There was a higher incidence of tremor (although not statistically significant) in men and of polyuria in women, but it is uncertain whether this reflected a real difference or only a difference in toleration or reporting e.g. men may notice and report tremor earlier because it interferes with their work.

There seems little doubt that, in an individual, side effects are related to higher plasma concentrations of lithium (i.e. in a longitudinal study), but in the present cross-sectional study those patients with side effects had lower plasma and erythrocyte lithium concentrations and a lower red cell/plasma lithium ratio. Presumably in clinical practice some individuals are more susceptible than others to develop side effects with lithium, and when this occurs the intake of lithium is reduced in an attempt to reduce the side effects; this results in a lower plasma lithium concentration. That a reduction of lithium intake was not revealed by a significant difference in prescribed dose between the two groups is not surprising, since the dose range was very large: also poorer drug compliance could have reduced the lithium intake in the side effects group, without its being reflected in the prescribed dose. However, assuming similar absorption and excretion, the ratio of plasma lithium to dose prescribed is an indication of compliance, and this ratio was not significantly different between the two groups. This relationship of side effects to plasma concentration of lithium may depend on the policy of the clinic; for instance, if the aim is to keep the plasma lithium above 1.0 mmol/l unless the patient suffers side effects (i.e. towards the upper limit of the therapeutic range), the plasma lithium concentration of many patients will need to be reduced (and hence results obtained as in this present study). However, if the aim is to keep the plasma lithium concentration at about 0.7 mmol/l (i.e. towards the lower limit of the therapeutic range), the plasma lithium concentration of few patients will be reduced because of side effects, and there may appear to be no relationship between side effects and plasma lithium concentration.

There has been considerable controversy about the value of the ratio of erythrocyte lithium to plasma lithium concentration. The red cell/plasma lithium ratio is probably dependent on the plasma lithium concentration (Ratey and Mallinger, 1977; Lee *et al*, 1975). Dorus *et al* (1975) found only a weak positive correlation between erythrocyte and plasma

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lithium concentration, whereas the present study shows a very strong positive correlation between the two and suggests that the ratio is relatively stable provided the dose of lithium is unchanged and also that the ratio does change with plasma lithium concentration. Our results therefore lend no support to the suggestion that individuals who show side effects have abnormally high erythrocyte lithium concentrations or abnormally high erythrocyte/plasma lithium ratios. Similarly, the erythrocyte lithium concentration was no more stable than the plasma lithium concentration, and therefore there seems to be little evidence to suggest that it is a more useful assay than plasma concentration.

Lithium side effects described in this study (Table II) usually occur at plasma levels within the therapeutic range (0.6–1.2 mmol/l), while more serious toxicity usually presents at levels above 2.0 mmol/l. Also, in long term lithium therapy there are several endocrine and metabolic effects, including alterations in thyroid metabolism, steroid metabolism, carbohydrate metabolism and inducement of nephrogenic diabetes insipidus. There is now increasing evidence that lithium even at therapeutic levels may produce renal lesions (Hestbech *et al*, 1977; Burrows *et al*, 1978) and irreversibly affect renal function (Bucht and Wahlin, 1978).

In this study there was little overall difference between patients receiving lithium as Priadel (controlled release preparation) and those receiving it as Camcolit (compressed tablets of lithium carbonate). The sex difference was simply a reflection of the preferences of psychiatrists who initiated therapy. The slight difference in mean dose and significantly lower plasma level in women on Priadel could have been a reflection, not of bio-availability, but of different patterns of ingestion, i.e. more patients on Priadel might have taken it as a single dose, and therefore the time from blood sampling to the previous dose might have been longer than if they had taken it in divided doses. However, this possibility seems unlikely, since only 5 out of 22 took it as a single dose, and of those 4 took it in the evening.

There was no significant difference in the incidence of side effects between the two preparations.

References

Bonting, S. L. (1970) Sodium-potassium activated adenosinetriphosphatase and cation transport. In *Membrane and Ion Transport*, (ed. E. E. Bittar) pp 257–63. New York: Wiley-Interscience.

Bucht, G. & Wahlin, A. (1978) Impairment of renal concentrating capacity by lithium. *Lancet*, *i*, 778–9.

Burrows, G. D., Davies, B. & Kincaid-Smith, P. (1978) Unique tubular lesion after lithium. *Lancet*, *i*, 1310.

Dorus, E., Pandey, G. N. & Davies, J. M. (1975) Genetic determinant of lithium ion distribution. *Archives of General Psychiatry*, **32,** 1097–1102.

Elizur, A., Shopsin, B., Gershon, S. & Ehlenberger, A. (1972) Intra: extracellular lithium ratios and clinical course in affective states. *Clinical Pharmacology and Therapeutics*, **18,** 947–52.

Frazer, A., Mendels, J., Secunda, S. K., Cochrane, C. M. & Bianchi, C. P. (1973) The prediction of brain lithium concentrations from plasma or erythrocyte measures. *Journal of Psychiatric Research*, **10,** 1–7.

Hesketh, J. E. (1976) Changes in membrane adenosine triphosphatase on administration of lithium salts *in vivo*. *Biochemical Society Transactions*, **4,** 328–30.

Hestbech, J., Hansen, H. E., Amdisen, A. & Olsen S. (1977) Chronic renal lesions following long-term treatment with lithium. *Kidney International*, **12,** 205–13.

Hewick, D. S., Newbury, P., Hopwood, S., Naylor, G. & Moody, J. (1977) Age as a factor affecting lithium therapy. *British Journal of Clinical Pharmacology*, **4,** 201–5.

Lee, C. R., Hill, S. E., Dimitrakoudi, M., Jenner, F. A. & Pollett, R. J. (1975) The relationship of plasma to erythrocyte lithium levels in patients taking lithium carbonate. *British Journal of Psychiatry*, **127,** 596–8.

Naylor, G. J., Dick, D. A. T., Dick, E. G. & Moody, J. P. (1974) Lithium therapy and erythrocyte membrane cation carrier. *Psychopharmacologia* (Berl.), **37,** 81–6.

Peet, M. (1975) The potential difference across the rectal mucosa during depressive illness and lithium therapy. *British Journal of Psychiatry*, **127,** 144–8.

Ratey, J. J. & Mallinger, A. G. (1977) The relationship between extra and intracellular lithium concentration in human red blood cells: an *in vitro* study. *British Journal of Psychiatry*, **131,** 59–62.

https://doi.org/10.1192/bjp.134.5.482 Published online by Cambridge University Press

SMITH, E. K. M. & SAMUEL, P. D. (1970) Abnormalities in the sodium pump of erythrocytes from patients with hyperthyroidism. *Clinical Science*, **38**, 49–61.

ZAKOWSKA-DABROWSKA, T. & RYBAKOWSKI, J. (1973) Lithium-induced EEG changes: relation to lithium levels in serum and red blood cells. *Acta Psychiatrica Scandinavica*, **49**, 457–65.

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