Pharmacology Biochemistry & Behavior, Vol. 13, pp. 205–208. Printed in the U.S.A.

Lithium Distribution Ratios in Psychiatrically Normal Subjects

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Received 3 March 1980

LIEBERMAN, K. W. AND P. STOKES. *Lithium distribution ratios in psychiatrically normal subjects.* PHARMAC. BIOCHEM. BEHAV. 13(2) 205–208, 1980.—Lithium was administered as the carbonate to 6 psychiatrically normal subjects for 11 days. The distribution of lithium between the erythrocytes and plasma, and the effect of exogenous lithium on intracellular and extracellular electrolytes was studied. The ratio of the concentrations of lithium in the erythrocytes and plasma was apparently lower in the normal group than in the patients diagnosed to have affective disorders.

Lithium Sodium Potassium Erythrocytes Manic-depressives Affective disorders

THE therapeutic efficacy of lithium (Li) in the treatment of mania is widely accepted [1] and the primary site of action of Li has been postulated to be the membrane. It has been suggested a defect exists in the membranal transport of electrolytes in cells of patients with affective disorders and Li may have an effect on the electrolyte transport abnormality [18]. Different investigators have discussed the possibility Li may act by stabilizing the membrane [24], altering various membrane functions [5] or substituting in a limited fashion for potassium (K) in stimulating sodium (Na) outflow from human erythrocytes [11].

As a consequence of the attention which has been given to cellular Li transport in affective disorder patients, the question must be raised pertaining to how psychiatrically normal controls handle Li. Information of this type is a requirement so that appropriate comparisons can be made between diseased and non-diseased states. There is a paucity of baseline data. Tupin *et al.* [31] administered Li to 4 male controls at a dosage of 1200 mg daily for the first 2 days and 900 mg daily for the last 2 days. More recent studies on normals include those done by Dorus *et al.* [7] and Ramsey *et al.* [26].

In this study we treated 6 psychiatrically normal controls with Li and studied the effect of exogenous Li on the intracellular (erythrocyte) and extracellular (plasma) electrolytes Na and K and the distribution of Li between erythrocytes and plasma.

METHOD

Li was administered 3 times daily for 11 days in the carbonate form to 6 psychiatrically normal controls at a total daily dosage level calculated to be in the range of 0.5–0.6 meq/kg body weight/day, the usual maintenance dose for manic patients being treated with Li. The normal volunteer group was composed of 5 females and 1 male ranging in age from 22–27 years with a mean age of 24.3 ± 1.8 years. Blood samples were drawn at 0900 hours before the first Li dose of the day was taken using Vacutainers with ammonium heparin as the anticoagulant, and plasma and erythrocytes were separated using the cobalt-60 salt of ethylenediaminetetraacetic acid (Co-60 EDTA) as an indicator of plasma entrapped in the erythrocyte fraction [4]. Ammonium heparin was required because of the possible contamination by sodium heparin of the endogenous Na.

Control (pre-Li) plasma and erythrocyte concentrations of Na and K in the psychiatrically normal subjects were determined by obtaining blood samples 3 times during a 7 day period prior to the initiation of the administration of Li.

Plasma and erythrocytes were analyzed for Li by atomic absorption spectrophotometry (Perkin-Elmer Model 503); Na and K by emission flame photometry (Instrumentation Laboratories Model 343). Plasma entrapped in erythrocytes were corrected for using the factor determined by Co-60 EDTA, which usually amounted to 2–3%.

RESULTS

The daily intracellular and extracellular Na, K and Li composition and the erythrocyte Li/plasma Li distribution ratio (E/P) are shown in Table 1. After the first day of Li treatment intracellular Na fell by 23.9% and intracellular K fell by 7.2%. The lowering of erythrocyte Na and K below control concentrations continued for the remainder of the time the subjects received Li.

The extent of the intracellular Na reduction during the course of Li administration was variable from day to day; a

TABLE 1

DAILY RECORD AND MEAN VALUES OF Na, K AND Li COMPOSITION OF EXTRACELLULAR (PLASMA) AND INTRACELLULAR (ERYTHROCYTE) FLUIDS AND E/P RATIOS OBTAINED FROM VOLUNTEER SUBJECTS DURING CONTROL (PRE-Li) AND Li ADMINISTRATION

	Plasma			RBC			
	Na	K	Li	Na	K	Li	E/P
Control* (Pre-Li)	139 ± 2	4.2 ± 0.4	0	7.1 ± 1.4	92.2 ± 2.0	0	—
Day							
1	139 ± 1	4.3 ± 0.1	0.43 ± 0.20	5.4 ± 1.1	85.6 ± 3.6	0.11 ± 0.03	0.28 ± 0.07
2	140 ± 2	4.4 ± 0.4	0.50 ± 0.14	6.5 ± 1.2	87.2 ± 4.3	0.17 ± 0.04	0.36 ± 0.12
3	141 ± 1	4.4 ± 0.2	0.56 ± 0.08	5.6 ± 1.4	85.5 ± 1.6	0.22 ± 0.05	0.40 ± 0.07
4	140 ± 2	4.0 ± 0.3	0.57 ± 0.09	5.0 ± 1.6	85.4 ± 3.7	0.23 ± 0.07	0.41 ± 0.09
7	140 ± 2	4.7 ± 0.2	0.54 ± 0.08	6.5 ± 0.5	87.7 ± 2.3	0.19 ± 0.07	0.36 ± 0.09
8	144 ± 2	4.4 ± 0.3	0.58 ± 0.12	6.0 ± 1.9	91.0 ± 4.2	0.20 ± 0.03	0.34 ± 0.06
9	142 ± 1	4.2 ± 0.3	0.59 ± 0.10	5.2 ± 1.1	87.9 ± 4.1	0.19 ± 0.06	0.32 ± 0.09
10	140 ± 2	4.0 ± 0.2	0.62 ± 0.16	5.6 ± 1.0	90.4 ± 0.9	0.21 ± 0.04	0.35 ± 0.07
11	140 ± 2	4.4 ± 0.4	0.61 ± 0.11	5.9 ± 1.6	87.7 ± 3.1	0.22 ± 0.03	0.36 ± 0.07
Mean	141 ± 2	4.3 ± 0.2	0.56 ± 0.06	5.7 ± 0.5	87.6 ± 2.0	0.19 ± 0.04	0.35 ± 0.04

All concentrations are expressed in units of meq/L and errors are given as standard deviations.
*Control period consisted of 3 samplings over a 7 day period.

maximum reduction was attained on Day 4 (29.6%) and a minimum reduction on Days 2 and 7 (8.5%). Mean reduction of erythrocyte Na from pre-Li levels was 19.7% for the 11 days of Li treatment ($p<0.01$ level). A less variable pattern was found for intracellular K; the largest drop occurred during the first 4 days of Li treatment and later rebounded to higher concentrations. Mean reduction in erythrocyte K during Li administration was 5.0% ($p<0.01$). There was no comparable alteration in plasma electrolytes; mean Na and K extracellular concentrations during Li treatment were similar to control values.

During Li administration plasma Li levels achieved stability on Day 3 and erythrocyte Li levels stabilized on Day 7. The E/P ratio maintained a constant value from Days 7–11, which was 0.35 ± 0.02. Including the E/P ratios from the period before the establishment of a constant value, the mean E/P ratio for the 11 days of Li treatment was 0.35 ± 0.04.

DISCUSSION

It has been suggested that abnormalities may exist in the systems regulating the transport of the monovalent cations Na, K and Li across cell membranes of manic-depressives [14, 17, 21, 22]. The data upon which this proposal was based used the erythrocyte as the model cell as we have done because of its accessibility and similarities in the monovalent cation transport mechanisms in this cell and the neuron [23,30]. Much *in vivo* erythrocyte based data concerning the distribution of administered Li between the intracellular and the extracellular compartments in various manic-depressive populations have been accumulated [6, 9, 15, 18–20, 25, 27–29]. The characteristics of monovalent cation transport across the erythrocyte membrane in a psychiatrically normal group which have been treated with Li is largely unknown. It is extremely important to be able to make comparisons using *in vivo* erythrocyte data between both patient and normal groups that have received Li so that the hypothesized membrane transport abnormality may be intensively studied. Though similar *in vitro* based erythrocyte Li data have been reported [25], *in vivo* experiments offer a physiologically more valid situation.

In our experiments Li was administered to psychiatrically normal subjects in the same dosages used in the treatment of manic-depressive illness. The E/P ratio was stable from the seventh day onwards until Li administration was stopped after the eleventh day. The mean E/P ratio for Days 7–11 for the 6 normals was 0.35 ± 0.02. This was the period during which equilibrium was maintained for Li distribution between the plasma and cell. Ramsey *et al.* [26] after 2 weeks of treatment found an E/P ratio of 0.35 ± 0.02 in his normal group consisting of 7 males and similarly Dorus *et al.* [7] gave 600 mg daily of Li to normal controls for 7 days. She reported a slightly lower E/P ratio for male normals (5 monozygotic and 5 heterozygotic twins), 0.28 ± 0.01. Furthermore, Dorus noted that the E/P ratio was constant with respect to time; 0.28 on the third day, 0.27 on the fifth day and 0.28 on the eighth day of Li treatment. A comparison of the E/P ratios obtained in our study with those of the other 2 reports corroborates our results. Since our normal group was largely composed of females (5 out of 6) and the remainder of the normals studied by others were exclusively male, there appears to be little significant variation in the E/P ratio on the basis of gender.

Li along with Na and K are alkali metals and it is reasonable to expect the physiological behavior of the Li ion is at least in some respects similar to Na and K ions. Li can be actively transported across cell membranes [33], but the rate of efflux from the cell was less than Na [16]. Extracellular K maintained some control over the rate of Na efflux [12]. It has been shown that the rate of removal of Na-22 from human erythrocytes was promoted by the presence of either K or Li in the extracellular test media [11], but K had a greater stimulatory effect upon Na efflux than Li. The suggestion has been made that Li activated in a manner similar to K the Na^+-K^+ activated Mg^{++}-dependent adenosine-

TABLE 2

IN VIVO E/P RATIOS FOR PSYCHIATRIC AND NORMAL CONTROL SUBJECTS

	Source	Mean *In Vivo* E/P	Categories
Psychiatric	Ramsey *et al.*[26]	0.47*	UP and BP
	Mendels and Frazer [18]	0.48*	R and NR
	Mendels and Frazer [19]	0.47†	A/D
	Flemenbaum *et al.* [9]	0.47†	A/D
	Sacchetti *et al.* [29]	0.52†	A/D
	Sacchetti *et al.* [29]	0.50†	A/D
	Mendels *et al.* [20]	0.55*	R and NR
	Rybakowski and Strzyzecoski [28]	0.56	A/D
	Casper *et al.* [6]	0.45*	R and NR
	Rybakowski *et al.* [27]	0.54	A/D
	Ramsey *et al.* [25]	0.50*	UP and BP
	Lieberman and Stokes‡	0.55	A/D
	Mean	0.51 ± 0.04	
Normal	Lieberman and Stokes, this paper	0.35	
	Dorus *et al.* [7]	0.28	
	Ramsey *et al.* [26]	0.35	
	Mean	0.33 ± 0.04	

UP: unipolar.
BP: bipolar.
R: responder.
NR: nonresponder.
A/D: affective disorder.
Errors are given as standard deviation.
*Calculated as the mean from either UP and BP or R and NR data.
†Calculated from a graph.
‡Lieberman and Stokes, unpublished data (1978).

triphosphatase transport system (Na-K ATPase), which was responsible for supplying the energy required for Na efflux [11,32].

Several investigators recently proposed some specific mechanisms by which Li is transported into or out of erythrocytes. Influx of Li into erythrocytes is said to be controlled by 3 mechanisms: transport linked to Na-K ATPase, Li-Na countertransport and passive diffusion. Only 2 mechanisms are suggested to be operative in Li efflux from the erythrocyte: passive diffusion and Li-Na countertransport [8, 10, 13].

Many investigators [6, 9, 18–20, 25–29] have determined the *in vivo* E/P ratio in various patient populations that were classified in numerous ways including unipolar or bipolar manic-depressives, responders and non-responders to Li treatment and affective disorder patients. We determined the E/P ratio in 133 affective disorder patients that were participating in our outpatient facility using the same blood separation and analytical techniques that were described in the methods section for the normal group [4]. Our mean E/P ratio was 0.55 ± 0.21 and ranged from a minimum value of 0.15 to a maximum value of 1.28. The results of the other investigators along with our data are summarized in Table 2. The E/P ratios for patients ranged from 0.45–0.56, and the mean for the lithium distributions ratios is 0.51 ± 0.04. Patient and normal controls values for the E/P ratio do not overlap. The E/P ratios for the normal group are confined to a limited range, while the patient groups are characterized by a broad range of E/P values. Because of the small size of the combined normal group in comparison to the much larger patient group it is impractical to make any statistical inferences. Also, the patient groups consist of a diagnostically heterogeneous population which complicates the problem of making comparisons and drawing specific conclusions. Even with these drawbacks it appears affective disorder groups have an *in vivo* E/P ratio that is higher than normal controls, 0.51 ± 0.04 vs 0.32 ± 0.04. Further extensive studies of the lithium distribution ratio in normal individuals are warranted to determine if the apparent sharply contrasting E/P ratios between normals and clearly defined well-diagnosed affective disorder patients is real. Conclusions of this type are supportive of the hypothesis that a defect exists in the mechanisms of ion transport in cells obtained from affective disorder patients.

When Li was administered to affective disorder patients erythrocyte Na remained unchanged or increased depending upon the daily Li intake [19]. Patients receiving greater than 1500 mg daily of Li improved and their erythrocyte Na increased by 13.8%; those on less than 1500 mg daily did not improve and their erythrocyte Na was stable [19]. Others have found that when patients received Li, responders to treatment had a greater increase in 24 hour exchangeable Na than non-responders [2,3]. Though these investigators used dissimilar methods [2, 3, 19] the results they achieved can be interpreted along the same lines; giving Li to patients diagnosed to have affective disorders led to an increase in intracellular Na in responders to the medication. The results we obtained for intracellular Na in normal controls contrasted with those found in patients, a 19.7% reduction in erythrocyte Na. No comparable data was available for

intracellular K in patients, but the normals experienced a 5.0% reduction in intracellular K. The differences in the effect of exogenous Li on intracellular Na in normal controls and patients is, also, supportive of the possibility of a defect in membrane ion transport in the affective disorder population.

The behavioral effects of Li in normal control subjects is not well known. Tupin *et al.* [31] reported members of his normal group experienced no negative reactions to Li and were fully capable of performing routine activities with one exception who complained about a slight decrease in energy. None of the normals found that Li produced any mood changes or sedation. Our control subjects were able to continue routine activities for the duration of the study, but some indicated that their handwriting became shaky and speech was slurred. By the end of the 11 day treatment most the subjects appeared to be mildly depressed and this depression disappeared within a short time after the end of the experiment.

ACKNOWLEDGMENT

This work was supported by the George F. Baker Trust and a gift from Mr. and Mrs. Paul Hexter.

REFERENCES

1. American Psychiatric Association Task Force. The current status of lithium therapy. *Am. J. Psychiat.* **132:** 997–1007, 1975.
2. Aronoff, M. S., R. G. Evans and J. Durell. Effect of lithium salts on electrolyte metabolism. *J. Psychiat. Res.* **8:** 139–159, 1971.
3. Baer, L., J. Durell, W. S. Bunney, Jr, B. S. Levy, D. L. Murphy, K. Greenspan and P. V. Cardon. Sodium balance and distribution in lithium carbonate therapy. *Archs gen. Psychiat., Chicago* **22:** 40–44, 1970.
4. Brading, A. F. and A. W. Jones. Distribution and kinetics of CoEDTA in smooth muscle and its use as an extracellular marker. *J. Physiol.* **200:** 387–401, 1969.
5. Bunney, W. E., Jr and D. L. Murphy. Neurobiological considerations on the mode of action of lithium carbonate in the treatment of affective disorders. *Pharmackopsychiat. Neuropsychopharmak.* **9:** 142–147, 1976.
6. Casper, R. C., G. Pandey, L. Gosenfeld and J. M. Davis. Intraerythrocyte lithium and clinical response. *Lancet* **2:** 418–419, 1976.
7. Dorus, E., G. N. Pandey and J. M. Davis. Genetic determinant of Li ion distribution; an in vitro and in vivo monozygotic-dizygotic twin study. *Archs gen. Psychiat. Chicago* **32:** 1097–1102, 1975.
8. Duhm, J., F. Eisenreid, D. F. Becker and D. Greil. Studies on the Li transport across red cell membrane. I. Li^+ uphill transport by Na^+-dependent Li^+ countertransport system. *Pflügers Arch. ges. Physiol.* **364:** 147–155, 1976.
9. Flemenbaum, A., R. Weddige and J. Miller. Li erythrocyte/plasma ratio as a predictor of response. *Am. J. Psychiat.* **135:** 336–338, 1978.
10. Frazer, A., J. Mendels and D. Brunswick. Transfer of Li^+ ions across the erythrocyte membrane. *Communs Psychopharmac.* **1:** 255–270, 1977.
11. Glen, A., M. Bradbury and J. Wilson. Stimulation of the sodium pump in the red blood cell by lithium and potassium. *Nature* **239:** 399–401, 1972.
12. Glynn, I. M. Na and K movements in human red cells. *J. Physiol.* **134:** 278–310, 1956.
13. Haas, M., J. Schooben and D. C. Tosteson. Coupling of lithium to sodium transport in human red cells. *Nature* **258:** 425–427, 1975.
14. Hokin-Neaverson, M., D. A. Spiegel and W. C. Lewis. Deficiency of erythrocyte Na pump activity in bipolar manic-depressive psychosis. *Life Sci.* **15:** 1739–1748, 1974.
15. Kantor, J., J. Kocsis, K. W. Lieberman and P. Stokes. Erythrocyte/plasma Li and maintenance treatment response. *New Res. Abstr., Am. Psychiat. Ass.:* NR 26, 1977.
16. Maizels, M. Cation transfer in human red cells. In: *Membrane Transport and Metabolism*, edited by A. Kleinzeller and A. Kotyk. New York: Academic Press, 1961, pp. 256–269.
17. Meltzer, H. L., S. Kassir, D. L. Dunner and R. R. Fieve. Repression of a Li pump as a consequence of lithium ingestion by manic-depressive subjects. *Psychopharmacology* **54:** 113–118, 1977.
18. Mendels, J. and A. Frazer. Intracellular lithium concentration and clinical response. *J. Psychiat. Res.* **10:** 9–18, 1973.
19. Mendels, J. and A. Frazer. Alteration in cell membrane activity in depression. *Am. J. Psychiat.* **131:** 1240–1246, 1974.
20. Mendels, J., A. Frazer, J. Baron, A Kukopulos, D. Reginaldi, L. Tondo and B. Caliari. Intraerythrocyte lithium ion concentration and longterm maintenance treatment. *Lancet* **1:** 966, 1976.
21. Naylor, G. J., D. Dick and E. Dick. Erythrocyte membrane cation carrier, relapse rate of manic-depressive illness and response to lithium. *Psychol. Med.* **6:** 257–263, 1976.
22. Naylor, G. J., D. Dick, E. Dick and J. Moody. Lithium therapy and erythrocyte membrane cation carrier. *Psychopharmacology* **37:** 81–86, 1974.
23. Post, R. L. ATPase as a participant in the active transport of sodium and potassium in the human erythrocyte. *J. biol. Chem.* **235:** 1796–1802, 1960.
24. Rafaelson, O. J., E. T. Mellerup and R. W. Schapiro. Lithium in the living organism. Is an integrated hypothesis possible? *Pharmakopsychiat. Neuropsychopharmak.* **9:** 108–115, 1976.
25. Ramsey, T. A., A. Frazer, W. L. Dyson and J. Mendels. Intracellular Li and clinical response. *Br. J. Psychiat.* **128:** 103–104, 1976.
26. Ramsey, T. A., A. Frazer, J. Mendels and W. L. Dyson. The erythrocyte Li/plasma Li ratio in patients with primary affective disorder. *Archs gen. Psychiat. Chicago* **36:** 457–461, 1979.
27. Rybakowski, J., M. Chtopocka and Z. Kapelski. Red blood cell Li index in patients with affective disorders in the course of Li prophylaxis. *Int. Pharmacopsychiat.* **9:** 166–171, 1974.
28. Rybakowski, J. and W. Strzyzewski. Red blood cell Li index and longterm maintenance treatment. *Lancet* **1:** 1408–1409, 1976.
29. Sacchetti, E., S. Bottinelli, L. Bellodi, R. Galasso and E. Smeraldi. Erythrocyte/plasma Li ratios. *Lancet* **1:** 908, 1977.
30. Skou, J. C. Further investigations on a (Mg^{++}-Na^+)-activated ATPase; possibly related to the active, linked transport of the Na-ion and the K-ion across the nerve membrane. *Biochim. Biophys. Acta* **42:** 6–23, 1960.
31. Tupin, J. P., G. K. Schlagenhauf and D. L. Creson. Lithium effects on electrolyte excretion. *Am. J. Psychiat.* **125:** 536–542, 1968.
32. Whittam, R. and H. P. Wheeler. Transport across red cells. *A. Rev. Physiol.* **32:** 21–60, 1970.
33. Zerahn, K. Studies on the active transport of lithium in isolated frog skin. *Acta physiol. scand.* **33:** 347–358, 1954.