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THE RELATIONSHIPS OF PLASMA AND ERYTHROCYTE SODIUM, POTASSIUM AND LITHIUM IN LITHIUM PROPHYLAXIS

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The relationship of intracellular Na^+ K^+ Li^+ to their extracellular concentrations had been studied on 22 cases of Bipolar affective disorders who had been on prophylactic lithium. 6 of these cases were non-responders who were admitted repeatedly despite a therapeutic serum lithium values of 0.8—1.1 m mol/L. Parameters measured were Plasma lithium (Lp), Erythrocyte Lithium (Le), Plasma potassium (Kp), Erythrocyte potassium (Ke) Plasma sodium (Nac). Eli had been calculated by using Nerst's equation. Significant correlations have been obtained for dosage and Lp, Lp and Le, and Lp and Le/Lp. There were no significant difference between the responders and non-responders as regards to values of Le, Lp, Nap, Nae, Kp and Ke.

In recent years there had been a number of promising reports that lithium transport characteristic in R.B.C. might be of value for predicting response in M. D. P. Maggs (1963) was the first to measure the R. B. C. lithium concentration in lithium treated patients. He found R. B. C. lithium to be lower than in plasma and observed some inter individual differences in R. B. C./plasma lithium ratio. The ratios ranged from 0.2 and 1. However, the ratio remained relatively stable, in each individual. The above lithium ratio had been the subject of much controversy regarding its usefulness as a clinical or research tool. Several authors have found that the R. B. C. lithium concentration and the lithium ratio could be related to clinical response and to the intensity of side effects of lithium therapy (Gasper *et al.*, 1976; Cazzulo and Smeraldi, 1975; Flemmingbaum *et al.*, 1978). There had been a suggestion that the ratio is genetically determined and possibly be a marker for affective illness (Dorus *et al.*, 1975; Sachtti *et al.*, 1977; Schless *et al.*, 1975; Mendlewicz and Berbanck 1977). Currently, in vitro methods had been developed by Rybakowski *et al.* (1976), Greil *et al.* (1977) and in order to establish the interconnections between various mechanisms of lithium transport across RBC membrane to the clinical states and reicomas of MDP illness.

The utility of such estimations remains to be established. However there are a number of contradicting views about the significance of Le and Lp, (Rybakowski *et al.* 1974; Lee *et al.* 1975; Ratey and Mallinger, 1977 and Mendels and Frazer, 1973). To complicate the situation further, there is no sound theoretical model to interpret the results. Only one such attempt has been made by Marini (1977).

The present study tries to find out the inter-relationship between plasma and erythrocyte lithium concentration and its application in clinical practice. The paper also tries to evaluate the possible correlation of the cation to the parameters of Na^+ and K^+.

MATERIALS AND METHODS

22 patients (17 males and 5 females) were randomly selected for the study. They had been on various dosage regi-

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mens of prophylactic lithium for a duration of more than 2 years in all cases (range 2.5 years to 7.5 years—Mean 5.4 years). They were considered to be good candidates for lithium prophylaxis according to the criteria of Schou and Thomson (1975). The diagnosis for the above patient were independently established by 2 psychiatrists using Feighner, criteria (1972). 6 cases were classified as non responders to lithium and were admitted repeatedly despite serum being within the range of 0.8-1.2 mmol/L.

BIOCHEMICAL METHODS

A morning sample of venous blood (4 ml) was collected for each patient 10-12 hours after last dose of lithium. The sample was processed for estimation of plasma lithium, by the procedure described by Coombs (1971) and for Na and K by the procedure described by Wooton (1964). The intra-cellular concentrations of Na^+ and K^+ and Li^+ was estimated by a modified procedure of Fortes Meyer and Starkey (1977) which has been adopted by Pradhan (1978). The equilibrium potential for Li^+ (Eli^+) was calculated by using standard Nearnt's equation at 37°C (Ganong, 1967).

RESULTS

The population criteria and the estimated parameters are tabulated (Table 1) below. It shows that there is no significant difference between the responders and non-responders as regards to Le, Lp, Nap, Nae, Kp and Ke.

A series of correlation coefficients between different parameters are shown in Table 2.

From the results, it is evident (1) between the dosage and body weight there is no correlation. (2) plasma lithium concentration has a significant correlation to the dosage and also the Le. Le/Lp are found to be dependent upon Lp level. These values are positively and negatively correlated to Lp level respectively (Table 2). The plot of Le and Lp (Fig. 1), has been drawn and also the correlation coefficient of

TABLE 1. *Population charcteristics* ($17M+5F$) *and the estimated parameters*

	Age/ (in years)	Body/ weight/ (in kg)	Dosage/ (in mg/ day)	Le	Lp	Nap	Nae	Kp	Ke
Responders ($N=16$)									
Range	20-40	39-72	600-1350	0.3-0.8	0.5-1.3	110-150	3-6.2	4-5	70-110
Mean	29	59.73	981.82	0.47	0.87	140.27	4.53	4.53	82.18
S.D.	6.22	12.16	292.39	.13	.32	8.17	.86	.37	9.39
Non Responders ($N=16$)									
Range	20-40	45-68	600-1200	.4—.8	.8—1.2	110-150	3-6	4-5	70-110
Mean	28	55.63	960.5	0.53	0.92	142.2	4.8	4.5	84.6
S.D.	6.6	6.6	298.2	.35	.35	9.62	.82	.32	9.41
t	0.33	0.36	0.15	0.95	0.32	0.47	1.55	0.18	0.54
p	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Student 't' test has been applied for the 2 categories, i.e. Responders & non-responders.

TABLE 2. *Correlation coefficients between different parameters both estimated and derived.*

Sl. no.	Parameters	No.	r	Inference
1.	Body weight and Dosage.	22	0.35	$p>0.05$
2.	Dosage and Lp	22	0.61	$p<0.01$
3.	Dosage and Le	22	0.69	$p<0.001$
4.	Lp and Le	22	0.84	$p<0.001$
5.	Lp and Le/Lp	22	—0.52	$p<0.05$

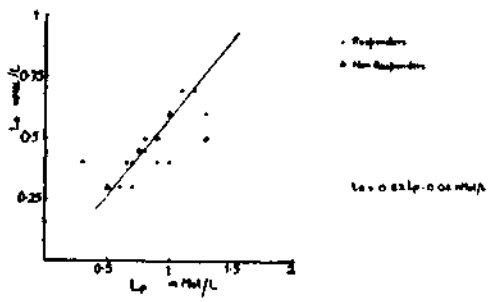

Fig. 1.

Le and Lp has been found to be of high statistical significance (Le=Lp×0.635—0.04 mmol/L) (Non-responders are marked as triangles) (3) The Le level had also significant correlation to dosages of lithium.

DISCUSSION

In this experimental study, significant correlations have been found for dosage and Lp level, dosage and Le level, Le and Lp level, and significant correlation for Lp and Le/Lp levels. No significant correlation between body weight and dosage could be obtained as the dosage of lithium are usually determined by the Lp level in the clinical practices. Hence it is likely that the plasma level has been found to be dependent upon the amount of lithium ingested and significantly the intracellular concentration depends upon the plasma lithium concentration also. Lee *et al.* (1975) have demonstrated that the Le level to be a non-linear function of Lp level.

In our study it is found that a linear regression line could be drawn for Le and Lp (Fig. 1). Lyttkene *et al.* (1976) have documented in agreement to the present finding that there is no significant deviation from a rectilinear relationship between erythrocyte and plasma lithium concentrations. The in vitro study of Ratey and Malinger (1977) supports this fact. But workers have been debating recently on the significance of Le/Lp ratio to its clinical implication Elizur *et al.* (1972), Cazullo and Smeraldi (1975) and Ramsey *et al.* (1976) have reported significant differences of Le/Lp for unipolar and bipolars. The Le/Lp ratio has also been correlated to antidepressant effect of lithium (Mendels *et al.* 1973, 1976). On the contrary, Lyttkens *et al.* (1976) have shown that there is sex difference in Le/Lp ratio and the value has been found to be highest for schizophrenic females and specifically more in elder age groups. Hence, it has been established that Le/Lp ratio is not at all an index of affectivity. Similarly Knorring *et al.* (1976) have disclaimed the Le/Lp of being any indicator of response to lithium. Rybakowski *et al.* (1974) have also demonstrated that Le/Lp is not related to age, sex, polarity of illness or clinical state rather Le has been found to be correlated with Lp value. Lee *et al.* (1975) have suggested an incorrect method of determining the relationship between Le and Lp. Unfortunately their equation turns out to be a quadratic one. In the present study the Le/Lp bears a significant relationship to Lp and is negatively correlated. The negative value means that the ratio proportionately decreases with increasing Lp, which is understandable in terms, of a linearity between Le and Lp (see equation in

Fig. 1) and Lp values are always greater than the Le values. From the above points, it is now apparent that any subdivision of M. D. P. as responders and non responders as Mendels and Frazer (1973) have proposed based on a high Le/Lp value seems to be invalid. In the present study authors did not find any difference for Le values for responders and non-responders. Also in the plot (Fig. 1) the non-responders lay close to the regression line. In the light of the high correlation coefficient for Le and Lp, authors are inclined to draw a conclusion that any dissection for responders and non-responders by erythrocyte Li^+ kinetics may not be the proper one. In the literature a better explanation regarding the Le/Lp ratio comes from Marini (1977) who has put the electro-diffusion model to lithium kinetics (Marini uses the term passive diffusion model). We have shown that lithium shows quite a variable nature in its uptake and release from erythrocytes with different half lives (Pradhan *et al.*, 1977, 1978 and 1980). It is very difficult to apply electro-diffusion model for lithium kinetics at this stage. Duhm *et al.* (1976) have demonstrated after a series of experiments that net uphill transport of lithium is dependent upon Na counter transport system. Coupling of lithium to Na transport has been reported by Hass *et al.* (1975). If simple electro diffusion could have been a sufficient condition for lithium distribution, then at a steady state plasma level or in vitro systems, the Le level should always be higher than Lp level, yielding approximately a value of 1.8 as Le/Lp ratio. But the values quoted in literature and the values of the present study lie far below unit, even the vitro studies do not show values of Le more than Lp. From the published Le/Lp ratio the calculated equilibrium potential is given in Table 3. The present study is incorporated in the table and it shows that our experimental value is one of the several values quoted in literature.

TABLE 3. *Equilibrium Potentials of Li (ELi)*

The experimental transmembrane potential for erythrocytes Lassen and Sten Knudsen (1968)		—11.3 to —14 mv
The calculated equilibrium potential of Li from the Le/Lp ratio published.		
1. Elizur *et al.*	(1972)	+35.977mv
2. Mendels and Frazer	(1973)	+19.052 mv
3. Lyttkens *et al.*	(1973)	+21.924 mv
4. Rybakowski *et al.*	(1974)	+16.457 mv
5. Lee *et al.*	(1975)	+11.506 mv
6. Present Study	(1982)	+17.207 mv

A positive ELi indicates that there is no free access of Li into the cell. Either the Li^+ conductance is very low due to membrane resistance or it is excluded out immediately once it becomes intracellular. A measured—11.3 mV to —14 mV membrane potential erythrocyte indicates that Li^+ has free accession to the cell for both the electrical and chemical gradient facilitates such an influx; but in clinical practice the equilibrium state is never reached. The efflux of Li^+ against its chemical gradient in vitro studies using erythrocyte may reveal the kinetic of such distribution.

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