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Relation between Erythrocyte and Plasma Lithium Concentrations as an Index in Psychiatric Disease

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ABSTRACT

In longitudinal and transverse studies, lithium was measured in plasma, serum and red blood cells (erythrocytes) of healthy male and female subjects as well as in patients of both sexes suffering from manic-depressive disease or schizophrenia. The results confirm that lithium in erythrocytes is lower than in plasma in all groups. The lithium concentration gradient between plasma and erythrocytes is not caused by a slow rate of diffusion through the erythrocyte membrane. The new result of the present study is the importance of sex, disease and age on the erythrocyte/plasma lithium ratio, which is significantly higher in female subjects with manic-depressive disease. This difference persists even during long-term lithium therapy. Older female schizophrenics also have a higher ratio of erythrocyte to plasma lithium than males of the same age. The findings emphasize the importance of endocrine investigation in mental disease and support the view that plasma lithium in humans does not always reflect the intracellular levels. The erythrocyte plasma ratio may also be of value in revealing diagnostic subgroups within the classical psychiatric framework.

INTRODUCTION

Even if lithium is assumed to be distributed mainly within intra- and extracellular water compartments of the body, its distribution is not uniform for several reasons. It can be transported actively through cell membranes and it influences and competes with several other ions such as sodium, potassium, calcium and magnesium. (For review, see Johnson, 1975 (11).) The distribution is strongly dependent on the lithium level in the plasma and possibly also on the duration of the lithium treatment. The therapeutic level of lithium is low and less than 1% of plasma sodium is exchanged for lithium. The lithium tissue/serum distribution ratios also unexpectedly exceed 1.0 in several tissues, such as muscle, bone, brain and kidney (21), although intracellular sodium is known to be low. In addition, since blood lithium varies rapidly between doses, and its transport into cells varies from tissue to tissue and is sometimes slow, part of the uneven distribution depends on the absence of a true distribution equilibrium.

Several reports have claimed that manic patients retain more lithium than healthy controls even after a single dose (1). This is the basis for attempts to link the clinical picture of patients receiving lithium and the erythrocyte/plasma concentration ratio. It has been preliminary reported that female manic-depressive patients had higher erythrocyte/plasma lithium ratio than healthy volunteers (14, 15), and that manic patients with acute attacks have such an elevated ratio (7). Correlations with response to treatment (4, 18) and with disease have been proposed (25), but also criticized (20). Part of the disagreement may derive from the observed dependence of the erythrocyte/plasma lithium ratio on the plasma lithium level (12). Fully aware of these difficulties, we further extended our previous material (14, 15) to include healthy male subjects and patients from both sexes with schizophrenia, in order to investigate whether or not some disagreement in the literature could be traced to distribution variations arising from differences in sex, age and disease; especially so, since preliminary findings revealed the possibility that differences in lithium distribution between erythrocytes and plasma are not exclusive to manic-depressive disease.

MATERIAL

The studies included longitudinal and transverse assays of lithium in plasma, serum and red blood cells. Lithium

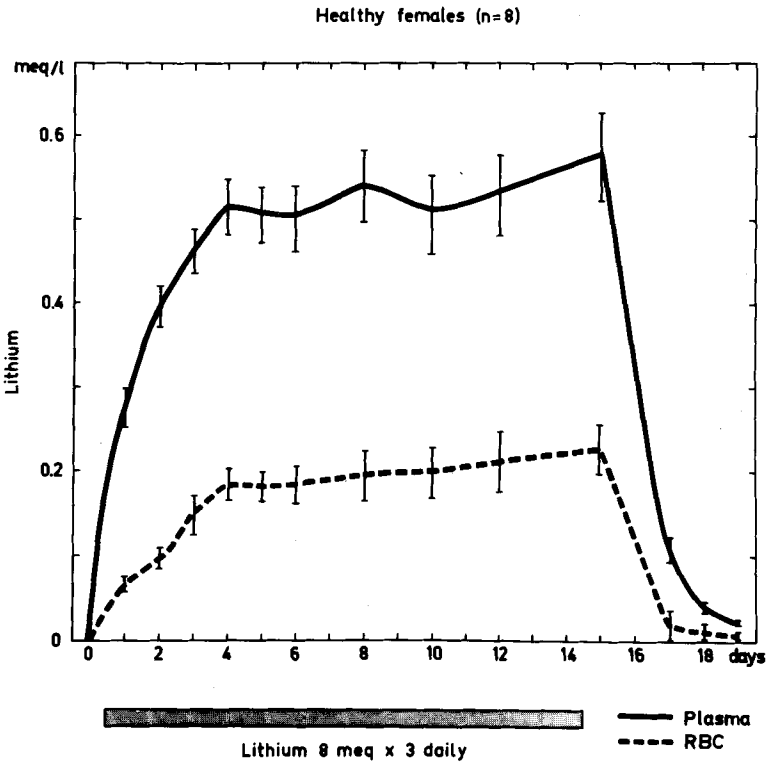

Fig. 1. Concentration of lithium in plasma and erythrocytes in 8 healthy females in response to lithium administration for 2 weeks.

was analysed with a Perkin-Elmer 306 atomic absorption spectrophotometer. Plasma and haemolysed blood were diluted 50 to 100 times for the analyses. The venous blood samples were drawn in the morning with the subjects fasting before the first dose of lithium was given. Lithium was administered as lithium carbonate. In the healthy individuals and in the patients comprising the longitudinal studies, a dose of 8 mEq three times daily was given. The patients comprising the transverse studies were given dosages that gave plasma levels between 0.6 and 1.2 mEq/l.

MATERIAL

Healthy persons

Two groups of apparently healthy subjects were examined, one comprising 8 female nurses and the other 8 male ambulance drivers from a hospital at Ludvika, Dalecarlia. Their ages varied between 20 and 40 years. No other medication than lithium was taken during the trial period. Blood samples were taken in the morning, twice before lithium was given and 13 times during the following 18 days. In addition the sedimentation rate, leukocyte count, platelet count, plasma creatinine and glucose in whole blood were assayed before, during and after the lithium test. There was no restriction in diet or special control of salt intake.

Patients

The patients were all treated at Ulleråker Hospital, Uppsala, Sweden. Thirty-seven patients with manic-depressive disease (23 women, 14 men) were examined; most of them had symptoms (in-patients), but some were in remission and were having lithium as prophylaxis (out-patients). Their ages ranged from 20 to 68 years. These patients had received lithium therapy for periods varying from 2 months to several years. A further 8 males and 8 females diagnosed as having chronic schizophrenia (in-patients) were treated in therapeutic trial at the hospital with dosages comparable to those given to the above-mentioned healthy subjects. Blood samples were taken in the same sequence as in the healthy subjects. The schizophrenic patients, however, also received their usual antipsychotic medication during the trial period. The diet was not restricted and there was no special control of salt intake.

RESULTS

Healthy subjects

During the test period lithium concentrations in plasma and erythrocytes followed the same time course, though the level was lower in erythrocytes than in plasma (see Fig. 1). A steady state between

Table I. *Half-lives ($T_{\frac{1}{2}}$) of lithium in plasma during the elimination phase*

Subjects	Number	Half-life (hours)
Healthy females	8	19±1
Healthy males	8	23±1
Schizophrenic females	8	19±2
Schizophrenic males	8	21±3

plasma and erythrocytes was rapidly attained, and no significant delay in the erythrocyte level was noted with the present sampling routine. The plasma levels reached 95% of the steady state within 4 days of treatment with lithium. After discontinuation of lithium therapy the half-life was computed from the slope of the concentration curve obtained during the elimination period the first point being the measurement 24 hours after the last dose. The half-lives thus obtained were not significantly different in the two sexes (men 23±2 and women 19±2 hours; Table I). Likewise the groups of healthy persons showed no sex difference (Table II). The sedimentation rate, leukocyte and platelet counts, creatinine in plasma and glucose in blood were not significantly affected by the lithium intake.

Patients

The relation between the erythrocyte and plasma levels of lithium in the manic-depressive patients of both sexes can be seen in Table II. Females with manic-depressive disease showed a probably significant higher erythrocyte/plasma ratio of lithium than healthy females ($p<0.05$) and manic-depressive males ($p<0.05$). The results of the longitudinal study have been taken from the last day of sampling in the steady state phase (Fig. 1). In the case of the manic-depressive patients, the day of sampling varied in relation to the first day of treatment, but in all cases the sampling was performed during the steady state. In this group, no classification was made according to the activity of the disease, the duration of lithium therapy or the age of the patients, since the numbers in each such subgroup would have been too small to permit reliable statistical analysis.

On the other hand, in the group of schizophrenic patients it was possible to select the patients so as to permit a further classification according to age. In the sample of schizophrenic patients there was no sex difference in the ratio of lithium in erythrocyte to lithium in plasma in the younger age groups (30–37 years), but in the higher age group this was considerably higher in the women (Table III). The half-lives of plasma lithium in the schizophrenic groups did not differ from those of the healthy volunteers, although the standard deviations were greater in the diseased than healthy subjects (Table I). In addition, we found in individual patients with schizophrenia and schizoaffective disease high levels of lithium in erythrocytes, and in 3 patients with the latter disease, the erythrocytes levels were repeatedly almost 100% of the plasma levels (16).

COMMENT

The results of this study confirm previous investigations (7, 8, 17, 19) that the concentrations of lithium in erythrocytes are lower than in plasma. The new result of the present study is the finding of the importance of sex, disease and age in affect-

Table II. *Distribution of lithium between plasma and erythrocytes at steady state*

Subjects	Number	Age (range)	Lithium mEq/l±SEM Plasma	RBC	$\frac{RBC \times 100}{Plasma}$
Healthy females	8	33 (23–47)	0.57±0.05	0.23±0.03	39±3
Healthy males	8	35 (23–49)	0.48±0.02	0.17±0.02	34±3
Manic-depressive females	23	38 (22–53)	0.66±0.04	0.34±0.03	50±4
Manic-depressive males	14	40 (23–66)	0.63±0.03	0.24±0.03	38±4

Table III. *Distribution of lithium (steady state levels) between plasma and RBC*

Subjects	Number	Age (range)	Lithium steady state mEq/l±S.E.M. Plasma	RBC	$\frac{RBC \times 100}{Plasma}$
Healthy females	8	33 (23–47)	0.53±0.12	0.20±0.08	38±3
Healthy males	8	35 (23–49)	0.47±0.06	0.17±0.05	34±3
Schizophrenic females	4	36 (35–37)	0.37±0.01	0.15±0.01	40±5
Schizophrenic females	4	60 (56–64)	0.66±0.10	0.37±0.10	52±7
Schizophrenic males	4	34 (30–37)	0.42±0.01	0.16±0.01	38±4
Schizophrenic males	4	61 (59–63)	0.49±0.01	0.16±0.03	32±3

ing the erythrocyte/plasma ratio. The difference in lithium concentration between plasma and erythrocytes cannot be attributed to a slow rate of diffusion through the erythrocyte membrane, at least not in our longitudinal studies in which the healthy subjects and schizophrenics were given lithium for 2 weeks. Although not fully conclusive, the results in the manic-depressive sample seem to indicate that the difference persists even during long-term therapy.

One possible explanation for the low levels of lithium in erythrocytes is that erythrocytes contain less water and that the lithium concentrations are only seemingly lower when measured in relation to the total blood cell volume. Since the water content of red blood cells is about 70% of that in plasma the difference found in this study between the lithium levels in plasma and erythrocytes can only partly be explained by a difference in distribution volume. Other explanations for the mechanism underlying the lower intracellular concentration must thus be sought, and possible candidates are the factors determining the transport and the difference between intra- and extra-cellular electrolyte concentration.

In the frog skin, there is an active sodium transport process by which sodium is transported from the outside to the inside of the skin. Here the lithium ion can be actively transported by this "sodium pump" and lithium thereby competes with sodium in the transport process (29). The lower content of lithium in erythrocytes indicates the presence of an active outward transport mechanism. The differences in erythrocyte/plasma ratio observed might then be explained by changes in the capacity of the transport mechanism, a situation that has also been postulated in patients with unipolar depression (19) and has been shown in bipolar manic-depressive psychosis (10). In this context it is worthy of note that the dog, which has a different sodium pump in the erythrocyte membrane than man, shows erythrocyte levels of lithium comparable to plasma levels (13). This postulated close relation between lithium and sodium transport mechanisms indicates that differences in sodium intake might explain our findings. As shown by Mendels and Frazer (19), a change in sodium intake might cause a change in erythrocytes and plasma levels of lithium, but the erythrocyte/plasma ratio will, however, remain unchanged. Thus the free salt diet cannot have been a source of error in our study. Preliminary evidence for genetic control of lithium ion distribution across erythrocyte cell membrane has been presented (6), indicating that our differences in erythrocyte/plasma ratio in manic-depressive women might be correlated to a great predisposition to manic-depressive illness. Lithium has also been shown to alter both calcium (27) and magnesium (3, 20) plasma levels. The significance of these changes is still unclear, but it is known that these two latter ions affect active transport of other ions, and it is conceivable that lithium may alter intracellular electrolyte concentrations in this way.

In the apparently healthy subjects, there was no sex difference in the erythrocyte/plasma lithium concentration ratio and in the group of schizophrenics, a sex difference was only found in the

older age group. The significance of this finding is not clear, but would seem to warrant a study of the possible effects of hormonal conditions on this ratio. In the present investigation we found two significant sex differences, one among the manic-depressives, where the women had a higher erythrocyte lithium level than the men, and the other among the schizophrenics previously mentioned. In addition to the differences in endocrine state, these findings could be caused by differences in disease pattern, patterns of physical activity, reaction of the patients to the symptoms, effects of hospitalization, diet and administration of other drugs. From all these possibilities, we favour the differences in hormonal factors between males and females as a primary cause, since there are clear indications that the endocrine status influences lithium distribution in animals (25), and the distribution of sodium both in humans and animals (2, 5, 28). The differences found in our study, however, may conceivably be related to specific differences in the erythrocytes, e.g. their age, and if this is the case they would not reflect the conditions in other organs in the body. Within the range of our assay, there is no significant deviation from a rectilinear relationship between the erythrocyte and plasma lithium concentration as in the work of Lee et al. (12), where the erythrocyte lithium was compared with plasma lithium over a wide range. In our study, it is not possible to explain the relative levels of lithium in erythrocytes as caused by differences in lithium concentration in the plasma.

Previously reported leukocytosis and changes in blood glucose found in patient samples (9, 17, 24) were not verified in the apparently healthy subjects in this study. Thus, these reported changes are unlikely to have been caused by the lithium intake alone, unless long-term treatment differs from a two-week test.

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