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Relationship between Plasma, RBC, and CSF Lithium Concentrations in Human Subjects

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Abstract. Simultaneous measurement of plasma, RBC, and plasma lithium concentrations took place with 17 inpatients chronically treated with lithium, at various times after the last lithium dose. RBC lithium levels were significantly higher than CSF lithium levels. Specimens drawn 10 or more hours after the last dose showed higher RBC and CSF lithium and lower plasma lithium than specimens drawn 4 or less hours after the last lithium dose. None of the lithium measurements differentiated manic-depressives from schizophrenics or schizoaffectives. Plasma, RBC, and CSF lithium all intercorrelated highly and equally.

The 'ideal prototype' for demonstrating the clinical value of drug plasma levels (1), plasma or serum lithium determination, nevertheless has distinct limitations: some patients develop toxicity at 'therapeutic' lithium levels (2), while others remain unaffected by 'toxic' levels (3). One plausible explanation arises from the known variability of lithium transport rates into different tissues, including the brain and blood erythrocytes.

Efforts to better predict the concentration of lithium at its active sites in the brain have led to the use of the red blood cell (RBC) lithium determination as a clinical parameter for monitoring lithium therapy (5). The basis for this practice derives partly from a study by *Frazer et al.* (6), who, after administering acute and chronic courses of lithium to rats, found that RBC lithium correlated with brain lithium more closely than did plasma lithium. Comparable data for humans, understandably difficult to obtain, appear nonexistent. Some researchers, however, have studied human cerebrospinal fluid (CSF) lithium as a parameter possibly more closely related to brain extracellular lithium than is plasma lithium (7). Less data is available on CSF than on RBC lithium, and no data appear available on the relationship between these two measures. Since both may have advantages over serum or plasma lithium as an access to brain

lithium, we decided to investigate the possible relationship between RBC, CSF, and plasma lithium levels.

Method

All subjects were inpatients bearing either manic-depressive, schizoaffective, or schizophrenic diagnoses, and all had been on oral lithium for at least 5 days prior to the study. Most subjects received concurrent medications, usually antipsychotics, and all subjects signed informed consent for the procedures.

CSF specimens, generally 4–6 cm^3, were obtained by routine lumbar puncture, yielding clear fluid free of gross blood. Blood specimens were obtained by concurrent venipuncture into EDTA-anticoagulated tubes. Lithium concentrations in CSF and plasma were determined by atomic absorption spectrophotometry, while RBC lithium concentrations were estimated by the indirect method of *Hisayasu et al.* (8), corrected for matrix error.

Results

Table I shows the corresponding plasma, RBC, and CSF lithium levels for all 17 subjects, along with age, sex, diagnosis, and time elapsed at sampling since last lithium dose.

Although the range of RBC lithim concentrations (0.11–0.66 mEq/l) largely includes the range of CSF lithium concentrations (0.03–0.38 mEq/l), the mean RBC lithium concentration (0.34 mEq/l) is significantly greater than the mean CSF lithium concentration (0.21 mEq/l), while the mean RBC:plasma lithium ratio (40%) is significantly greater than the mean CSF:plasma lithium ratio (24%) according to two-tailed t-tests for correlated measures ($p < 0.001$ and $p < 0.01$, respectively).

Comparing results for specimens obtained 1–5 h after the last lithium dose, with those obtained 10–18 h after the last dose, we found that at the later sampling time, the plasma levels tended to be lower (0.30 vs. 0.98 mEq/l), the RBC levels higher (0.36 vs. 0.32 mEq/l), the RBC:plasma ratio higher (45 vs. 32%), the CSF levels higher (0.23 vs. 0.18 mEq/l), and the CSF:plasma ratio higher (28 vs. 18%), although only the last difference reached significance ($p < 0.001$) according to a t-test for independent scores.

None of these four lithium parameters appeared to differentiate the three main diagnostic groups (manic-depressive, schizoaffective and schizophrenic); with one-way analysis of variance, none of the diagnostic differences approached significance.

Table I. Plasma, RBC, and CSF lithium levels in subjects tested

Subject No.	Sex	Age	Diagnosis[1]	Time[2]	Plasma lithium	RBC lithium	RBC: plasma ratio	CSF lithium	CSF: plasma ratio
					mEq/l	mEq/l	%	Meq/l	%
1	F	38	M–D	1	0.78	0.22	28	0.03	4
2	F	58	S	13	0.85	0.60	70	0.25	29
3	M	20	S	16	0.67	0.28	42	0.17	25
4	F	34	S–A,E	17	0.59	0.45	76	0.16	27
5	F	52	S	18	1.02	0.55	54	0.28	27
6	M	25	M–D	1	1.76	0.66	37	0.37	21
7	M	26	M–D	1	1.02	0.31	30	0.17	17
8	M	19	S	4	0.93	0.31	33	0.23	25
9	M	34	S–A,D	2	1.03	0.31	30	0.20	19
10	F	21	S–A,E	4	0.69	0.28	41	0.10	14
11	F	24	S	1	0.68	0.18	26	0.16	24
12	M	48	S–A,D	10	0.66	0.19	29	0.18	27
13	M	41	M–D	10	0.72	0.21	29	0.25	35
14	M	18	S	10	0.67	0.15	22	0.20	30
15	F	22	S	14	1.30	0.62	48	0.38	29
16	F	19	M–D	13	0.46	0.11	24	0.14	30
17	F	32	S–A,D	10	1.01	0.39	39	0.26	26

[1] Diagnosis code: M–D = manic-depressive, manic or mixed (case No. 1); S–A,E = schizoaffective, excited; S–A,D = schizoaffective, depressed; S = schizophrenic, other (paranoid, undifferentiated, or unspecified).
[2] Time = time in hours since last dose of lithium.

Finally, plasma, RBC, and CSF lithium concentrations all showed equally significant ($p < 0.001$) Pierson product-moment intercorrelations: 0.72 for RBC vs. CSF; 0.74 for plasma vs. CSF; and 0.74 for plasma vs. RBC.

Discussion

Much of our data corroborates previous findings. Both our CSF lithium concentrations and our CSF: plasma ratios agree fairly well with what others have found (7,9–15). Previous results (4, 13) would also predict the observed effects of the time elapsed since the last dose. Like others (7, 10), we failed to find any relationship of diagnosis to CSF lithium or CSF:plasma lithium ratio.

As far as we can determine, our study is the first to report concurrent measurement of plasma, RBC, and CSF lithium, with somewhat surprising results emerging from their intercorrelations. Merely from the fact that RBC and CSF lithium concentrations rise and fall more slowly following a dose of lithium, than does plasma lithium concentration (4, 6), one might predict a closer correspondence of CSF with RBC than with plasma lithium, especially in a study where the time factor varied from subject to subject. That this failed to occur, together with the fact that RBC lithium proved significantly higher than CSF lithium, supports the hypothesis that transfer of lithium into and out of the CSF and RBC takes place by different mechanism. In fact, considerable experimentation (16, 17) has now established several mechanisms of lithium transport by the RBC membrane, while the more scanty data (18, 19) on lithium transfer to and from the CSF suggest that this occurs primarily by bulk flow and simple diffusion. Moreover, a study of rats (20) showed no advantage for CSF over serum lithium as a predictor of brain lithium, while CSF lithium in humans has also failed to predict the therapeutic effect (7, 15).

It may be possible to speculate that CSF lithium, as a possible indicator of brain extracellular lithium, may yet have clinical value. If RBC lithium uptake has validity as a model for intraneuronal uptake in the brain, then brain extracellular lithium, rather than plasma lithium, may provide the pertinent milieu in which neuronal lithium uptake occurs. Therefore, simultaneous consideration of CSF lithium, as a model for brain extracellular lithium, and RBC lithium as a model for cellular lithium uptake, might improve our ability to estimate actual intraneuronal levels of lithium in the brain and eventually allow an understanding of differences in patient response.

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