Original paper

Archives of Psychiatry Research 2025;61:249-254

DOI:10.20471/.dec.2025.61.03.06
Received Oct 25, 2025
Accepted after revision Sept 26, 2025

Lithium Across Saliva, Plasma, and Erythrocytes and Its Links to Electrolytes/ Renal Markers in the First Treatment Week

Darko Vlahović[1,2], Mislav Škrobo[1], Frane Paleka[1], Dalibor Karlović[1,2], Zoran Karlović[3], Vjekoslav Peitl[1,2]

[1]Department of Psychiatry, University Hospital Center Sestre Milosrdnice, Zagreb, Croatia, [2]School of Medicine, Catholic University of Croatia, Zagreb, Croatia, [3]School of Dental Medicine, University of Zagreb, Zagreb, Croatia

Keywords

Lithium; saliva; erythrocytes; electrolytes; creatinine

Abstract

Aim: To determine whether lithium concentrations measured in saliva, plasma, and erythrocytes at a standardized morning time (09:00) after brief exposure are associated with plasma potassium, sodium, and creatinine. **Subjects and Methods:** Seventy-seven inpatients or day-hospital patients with bipolar disorder, treatment-resistant depression, or depression with high suicide risk received oral lithium carbonate 600 mg/day for five days. On day 6 at 09:00, unstimulated saliva, plasma, and erythrocyte samples were collected. Lithium was quantified using spectrophotometric assay. Potassium, sodium, and creatinine were obtained from blood at the same visit. Statistical analyses were conducted using multiple linear regression. **Results:** Models for potassium ($R^2 = 0.086$; $p = 0.497$) and sodium ($R^2 = 0.058$; $p = 0.662$) were not significant. For creatinine, the model explained a modest proportion of variance ($R^2 = 0.252$) and was non-significant ($p = 0.053$). Within this model, plasma lithium showed the largest (negative) standardized coefficient ($\beta = –0.437$; $p = 0.057$), whereas saliva ($\beta = 0.323$; $p = 0.096$) and erythrocytes ($\beta = –0.152$; $p = 0.467$) were not significant. **Conclusion:** In the first treatment week, lithium in saliva and erythrocytes was not associated with plasma potassium or sodium and added little beyond plasma lithium for explaining creatinine. These early, single-time-point findings support plasma as the reference matrix and motivate larger, longitudinal, multi-time-point studies pairing noninvasive sampling with renal covariates.

Introduction

Lithium remains the cornerstone mood stabilizer for the treatment and prevention of bipolar disorder [1]. Although its clinical efficacy is well established, safe and effective use depends on careful therapeutic monitoring [2]. Standard practice focuses on plasma (or serum) concentrations, yet lithium distributes across multiple biological compartments, and matrix-specific determinants, such as epithelial transport in salivary glands or membrane transport and ionic gradients in erythrocytes, may shape measured levels and their physiological relevance [2-4].

Beyond exposure, kidney function and electrolyte homeostasis are central to lithium's disposition. Lithium is

Correspondence to:
Darko Vlahović
University Hospital Center Sestre
Milosrdnice, Department of Psychiatry
Vinogradska 29, Zagreb, Croatia
E-mail: dvlahovic01@gmail.com

cleared almost exclusively by the kidneys, and elements of its tubular handling overlap with mechanisms governing sodium and, to a lesser extent, potassium balance [5,6]. In this context, previous studies have shown that serum creatinine and serum potassium are correlated with serum lithium levels [7,8]. These observations, together with lithium's effects on renal concentrating ability and water-electrolyte balance, make it plausible that lithium measured in different matrices could be associated with variation in plasma sodium and potassium, and relate to creatinine as a routine indicator of renal function [9,10].

Nevertheless, prior evidence is heterogeneous. Many studies examine a single matrix (typically serum/plasma), use nonstandardized sampling times, or do not assess cellular compartments that may better reflect intracellular exposure [11,12]. Saliva offers a noninvasive alternative suitable for frequent sampling, but its relationship to plasma and cellular lithium may vary with salivary flow, pH, and glandular transport dynamics [8,13]. Erythrocytes provide a cellular window on lithium handling, yet their incremental value over plasma for interpreting physiological markers remains uncertain [4,14,15]. Clarifying how these matrices relate to key physiological markers of fluid-electrolyte and kidney homeostasis could refine laboratory interpretation, support noninvasive monitoring strategies, and inform individualized dosing [8,16,17].

Given this background, the present study sought to characterize the relationships between lithium concentrations in saliva, plasma, and erythrocytes and plasma concentrations of potassium, sodium, and creatinine under a fixed 09:00 collection. Our primary objective was to determine the extent to which lithium measured across matrices explains variability in plasma sodium and potassium. A secondary objective was to evaluate associations with creatinine as a proxy for renal function. We used multiple linear regression to estimate the unique contribution of each matrix.

Mapping these cross-matrix relations may refine interpretation when results are borderline, amid fluctuating renal function, or venipuncture is impractical.

Subjects and Methods

Participants were enrolled from the Clinical Department of Psychiatry, University Hospital Center Sestre milosrdnice (Zagreb, Croatia), either during inpatient admission or within the day-hospital program of this tertiary-care institution. In total, 77 individuals were included. Eligibility required a confirmed diagnosis of bipolar disorder, treatment-resistant depression, or depression with a marked suicide risk, and recent initiation of oral lithium carbonate at a total daily dose of 600 mg (300 mg at 9:01 AM and 300 mg at 9:00 PM) for five consecutive days. We excluded persons with factors that could compromise normal salivation (e.g., active oral infections, xerostomia), pregnant individuals, and patients taking medications known to influence plasma lithium concentrations (non-steroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, metronidazole). Additional exclusions were dehydration, hyponatremia, diabetes, renal impairment, thyroid disease, alcohol dependence, and significant heart disease. All participants provided written informed consent after a thorough explanation of study aims and procedures. The protocol was approved by the Ethics Committee of the University Hospital Center Sestre milosrdnice (Zagreb, Croatia; approval No. 251-29-11-24-03).

Clinical evaluation and study design was as follows: between August and December 2024, patients admitted either to inpatient ward or the day hospital who had confirmed diagnoses of bipolar disorder, treatment-resistant depression, or depression with a marked risk of suicide were enrolled. A psychiatrist established the diagnoses according to ICD-11 criteria, drawing on the Mini-International Neuropsychiatric Interview (MINI), a structured diagnostic tool [18,19]. Clinical data collection was performed on the same day as biospecimen sampling, potassium, sodium and creatinine blood levels were obtained via blood draw.

After five days of oral lithium carbonate (600 mg/day), saliva, plasma, and erythrocyte samples were collected at 09:00 on day 6. Unstimulated saliva was obtained with Salivette® (120 s; no chewing/citric acid; ≥ 1 h abstinence from food/drink/smoking/oral hygiene), then centrifuged and analyzed immediately. Whole blood obtained for lithium quantification (K_3EDTA) was processed to plasma by centrifugation and to erythrocyte lysate by mixing equal volumes of blood and distilled water (500 μL) followed by 10 min centrifugation. Lithium was quantified on an Architect c8000 analyzer (Abbott) using the manufacturer's spectrophotometric assay.

In terms of statistical analysis, sample size was determined a priori with G*Power software, while the data was analysed in SPSS v20 using multiple linear regression.

Results

Association with plasma potassium

We tested whether lithium concentrations in saliva, plasma, and erythrocytes were associated with plasma potassium using multiple linear regression (potassium as the dependent variable). The model explained little variance ($R^2 = 0.086$) and was not statistically significant ($p = 0.497$). None of the individual predictors reached significance. These findings indicate no evidence of an association between lithium levels in any matrix and plasma potassium in this cohort. Regression coefficients are shown in Table 1.

Table 1. Coefficients from the multiple linear regression in which the dependent variable is plasma potassium concentration and the predictor variables are lithium concentrations in saliva, plasma, and erythrocytes

Variable	B	stand. error	β	t	p
Saliva	0.037	0.130	0.059	0.284	0.778
Plasma	-0.870	0.578	-0.366	-1.507	0.144
Erythrocytes	1.189	1.067	0.253	1.114	0.275

B - unstandardized regression coefficient; Stand. error - standard error; β - standardized regression coefficient; t - t value; p - p value; statistical significance $p < 0.05$.

Table 2. Coefficients from the multiple linear regression in which the dependent variable is plasma sodium concentration and the predictor variables are lithium concentrations in saliva, plasma, and erythrocytes

Variable	B	stand. error	β	t	p
Saliva	0.877	0.747	0.246	1.175	0.251
Plasma	-2.854	3.326	-0.212	-0.858	0.399
Erythrocytes	1.797	6.146	0.068	0.292	0.772

B - unstandardized regression coefficient; Stand. error - standard error; β - standardized regression coefficient; t - t value; p - p value; statistical significance $p < 0.05$.

Table 3. Coefficients from the multiple linear regression in which the dependent variable is creatinine concentration and the predictor variables are lithium concentrations in saliva, plasma, and erythrocytes

Variable	B	stand. error	β	t	p
Saliva	7.913	4.576	0.323	1.729	0.096
Plasma	–40.541	20.384	–0.437	–1.989	0.057
Erythrocytes	–27.831	37.670	–0.152	–0.739	0.467

B - unstandardized regression coefficient; Stand. error - standard error; β - standardized regression coefficient; t - t value; p - p value; statistical significance $p < 0.05$.

Association with plasma sodium

To examine potential electrolyte interrelationships, we performed multiple linear regression with plasma sodium as the dependent variable and lithium concentrations in saliva, plasma, and erythrocytes as predictors. The model explained little variance ($R^2 = 0.058$) and was not significant ($p = 0.662$). No individual predictor reached significance; the largest standardized effect was for salivary lithium ($\beta = 0.246$, $p = 0.251$). Full regression coefficients are shown in Table 2.

Association with plasma creatinine

We evaluated whether lithium concentrations in saliva, plasma, and erythrocytes were associated with plasma creatinine using multiple linear regression with creatinine as the dependent variable. The model explained a modest proportion of variance ($R^2 = 0.252$) and was non-significant ($p = 0.053$). Full coefficients are provided in Table 3.

Discussion

In this study we examined whether lithium concentrations measured in saliva, plasma, and erythrocytes re-

late to plasma potassium, sodium, and creatinine under a standardized morning sampling schedule (09:00) after short-term lithium administration. Across models, lithium levels showed no association with plasma potassium or sodium, and there was a trend toward an inverse association between plasma lithium and creatinine that did not reach statistical significance; the overall creatinine model explained a modest proportion of variance (R^2 = 0.252). These findings indicate that, within this early treatment window and sampling framework, salivary and erythrocyte lithium do not add explanatory value for electrolyte levels and offer limited incremental information for renal markers beyond plasma lithium.

In line with evidence that clinically meaningful renal effects accrue over months to years, our week-one analyses showed no associations with sodium or potassium and a creatinine model that did not reach statistical significance (R^2 = 0.252; p = 0.053), consistent with minimal short-term change. Adolescent inpatient cohorts followed during lithium treatment did not exhibit significant deterioration in creatinine-based renal measures over the observation period, despite expected endocrine and hematologic shifts, supporting the notion that clinically meaningful renal effects typically emerge over longer periods [20]. By contrast, a meta-analysis of adult cohorts that combined longitudinal and cross-sectional data found a small yet statistically significant increase in serum creatinine with sustained lithium therapy (≈7 μmol/L over ~64 months; ≈1.6 μmol/L/year), indicating that lithium-associated renal change is gradual and cumulative rather than immediate [21]. These early-window results should be interpreted alongside population-based evidence on long-term renal outcomes.

Complementing our early-window findings, a nationwide retrospective cohort from Iceland reported a concentration-dependent increase in incident stage ≥ 3 chronic kidney disease among lithium-treated individuals with mood disorders. Compared with a control group of patients with mood disorders not receiving lithium, risk rose stepwise with mean blood lithium concentration: HR 2.93 (95 % CI 1.97 – 4.36) for 0.60 – 0.79 mmol/L and HR 4.31 (2.66 – 6.99) for 0.80 – 0.99 mmol/L, whereas 0.30 – 0.59 mmol/L was not significantly different (HR 1.22, 0.78 – 1.90). Age, baseline renal function, diabetes, and prior AKI were additional risk factors. These registry data support the view that lithium-related renal effects are small in the short term but accrue over years, and they reinforce practice recommendations to monitor levels closely and use the lowest effective dose, which is fully consistent with the absence of robust electrolyte or creatinine signals in our 6-day design [22].

In relation to prior work, Parkin et al. reported a strong saliva-serum lithium correlation across 169 paired samples from 75 patients (unadjusted r = 0.74; covariate-adjusted r = 0.77 after accounting for daily dose, diabetes, and smoking) and showed that within-patient saliva/serum ratios can predict serum lithium well, especially when averaging three prior visits (r = 0.90) over longitudinal follow-up up to 18 months. They observed no association with sodium or creatinine, but did find modest positive correlations between lithium (saliva and serum) and potassium. In our short-term, single-time-point design after brief exposure, we likewise found no relationship with sodium and no robust link with creatinine (only a borderline, negative partial association for plasma lithium), whereas we did not detect an association with potassium. Differences in sampling and analysis (passive drool and ICP-OES vs. Salivette® collection and spectrophotometry), study horizon (longitudinal multi-visit vs. one standardized morning time-point), and covariate handling likely account for the discrepant potassium finding. Taken together, Parkin's longitudinal evidence supports salivary lithium as a feasible monitoring matrix when calibrated within individuals, while our early-phase data suggest saliva offers limited incremental information about electrolytes or creatinine beyond plasma at a single trough time-point [8].

The absence of relationships with sodium and potassium in our data is consistent with heterogeneity across prior reports. In a retrospective multivariable analysis of a Chinese Han cohort (N = 186), serum lithium was negatively associated with sodium in adjusted models and positively correlated with creatinine in unadjusted analyses; potassium was not examined as an independent predictor. These patterns likely reflect differences in population characteristics, sampling times, dosing, and covariate adjustment [7]. Our standardized single-time-point design and brief exposure period likely reduced the opportunity to detect electrolyte-lithium covariation that may emerge with chronic tubular effects or with greater variation in volume status and sodium-water balance.

Pharmacokinetic considerations provide a coherent framework for interpreting these results. Population pharmacokinetic syntheses consistently identify renal function and body size as the most robust determinants of lithium clearance, with age exerting context-dependent effects [23]. Matrix-to-matrix relationships, such as saliva versus plasma, can vary across study designs and patient characteristics, which helps explain why noninvasive matrices added little beyond plasma at a single trough [8]. In that light, it is unsurprising that plasma lithium emerged as the strongest, albeit non-significant, predictor in our creatinine model, while salivary and erythrocyte lithium contributed little once shared variance was accounted for. The possibility of collinearity among matrices may further attenuate individual coefficients, limiting power to detect unique effects when

predictors are physiologically linked. Several features of the study design may explain the pattern of findings. Sampling occurred early in treatment at a fixed morning time, capturing a relatively constrained exposure range and minimizing diurnal and post-dose fluctuations; under such conditions, any renal or electrolyte perturbations attributable to lithium are expected to be small [21,24]. Because doses were not modified during the observation window, the negative partial association between plasma lithium and creatinine is more plausibly attributable to multicollinearity among matrices and short-term, unmeasured determinants (e.g., hydration status, minor timing variability, analytic noise) than to clinical titration. Finally, while saliva remains a promising noninvasive matrix for therapeutic monitoring, its relation to plasma and cellular lithium depends on flow rate, pH, and glandular transport, which may limit incremental explanatory value for systemic physiological markers in a short-term, single-time-point design [25]. These considerations are consistent with pharmacokinetic work emphasizing renal function and body size as principal drivers of lithium handling and underscore the need for carefully controlled, multi-time-point comparisons across matrices [23,26].

Clinically, our data reinforce two practical messages. First, for short-term safety assessment and exposure monitoring, plasma remains the reference compartment; salivary measurements may facilitate noninvasive sampling but did not improve the explanation of electrolyte or creatinine variability in this protocol [8,17]. Second, given meta-analytic evidence of small long-term increases in creatinine with chronic therapy, routine renal monitoring remains essential, particularly as treatment duration lengthens and intercurrent factors (e.g., age, body size, comedications affecting sodium-water balance) accumulate [17,21]. This study has limitations that warrant cautious interpretation of the findings. It was single-center with restricted exposure duration; it did not explicitly model additional renal covariates. Potential collinearity among matrices may have reduced sensitivity to detect unique associations, and single-timepoint sampling cannot capture dynamic relationships that evolve across a dosing interval or over months of therapy. Nonetheless, the standardized protocol, multi-matrix sampling, and prespecified multivariable approach offer a clear snapshot of early treatment physiology that complements longer-term observational evidence.

In summary, within a standardized morning sampling framework after brief lithium exposure, lithium concentrations in saliva and erythrocytes were not associated with plasma potassium or sodium and added little information for creatinine beyond plasma lithium. The non significant negative association between plasma lithium and creatinine likely reflects study timing, shared variance among matrices, and short-term, unmeasured factors rather than a robust causal effect. Future work should extend follow-up, incorporate body-mass covariates alongside renal function measures, and evaluate matrix relationships across full dosing intervals to determine whether noninvasive sampling can meaningfully augment plasma-based monitoring in routine care.

Acknowledgments

None.

Conflict of interest

None to declare.

Funding Sources

None.

References

1. Carli M, Weiss F, Grenno G, Ponzini S, Kolachalam S, Vaglini F, et al. Pharmacological strategies for bipolar disorders in acute phases and chronic management with a special focus on lithium, valproic acid, and atypical antipsychotics. Curr Neuropharmacol. 2023;21:935-50.
2. Nederlof M, Heerdink ER, Egberts ACG, Wilting I, Stoker LJ, Hoekstra R, et al. Monitoring of patients treated with lithium for bipolar disorder: an international survey. Int J Bipolar Disord. 2018;6:12.
3. Serdarević N, Kozjek F, Malešič I. Saliva and serum lithium monitoring in hospitalized patients and possibility to replace serum to saliva. Bosn J Basic Med Sci. 2006;6:32-5.
4. El Balkhi S, Megarbane B, Poupon J, Baud FJ, Galliot-Guilley M. Lithium poisoning: is determination of the red blood cell lithium concentration useful? Clin Toxicol (Phila). 2009;47:8-13.
5. Girardi P, Brugnoli R, Manfredi G, Sani G. Lithium in bipolar disorder: optimizing therapy using prolonged-release formulations. Drugs R D. 2016;16:293-302.
6. Alsady M, Baumgarten R, Deen PMT, de Groot T. Lithium in the kidney: friend and foe? J Am Soc Nephrol. 2016;27:1587-95.
7. Xu YY, Xia QH, Liang J, Cao Y, Shan F, Liu Y, et al. Factors related to lithium blood concentrations in Chinese Han patients with bipolar disorder. Neuropsychiatr Dis Treat. 2019 Jul 10;15:1929-37.
8. Parkin GM, McCarthy MJ, Thein SH, Piccerillo HL, Warikoo N, Granger DA, et al.

Saliva testing as a means to monitor therapeutic lithium levels in patients with psychiatric disorders: identification of clinical and environmental covariates, and their incorporation into a prediction model. Bipolar Disord. 2021;23:679-88.
9. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord. 2016;4:27.
10. Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: a literature review of approaches to clinical management and risk stratification. BMC Nephrol. 2018;19:305.
11. Sheikh M, Qassem M, Triantis IF, Kyriacou PA. Advances in Therapeutic Monitoring of Lithium in the Management of Bipolar Disorder. Sensors (Basel). 2022;22:736.
12. Köhler-Forsberg O, Wiuff AC, Devantier TA, Østergaard SD, Faraone SV, Nierenberg AA. Estimating the 12-hour serum lithium level (eli12): development and two proof-of-concept studies. J Clin Psychiatry. 2025;86:24m15547.
13. Resztak M, Czyrski A, Sobiak J. Saliva as a matrix for therapeutic drug monitoring and disease biomarkers in children and adolescents. Pharmacol Rep. 2025;77:921-61.
14. Kato T, Shioiri T, Inubushi T, Takahashi S. Brain lithium concentrations measured with lithium-7 magnetic resonance spectroscopy in patients with affective disorders: relationship to erythrocyte and serum concentrations. Biol Psychiatry. 1993;33:147-52.
15. Lavonas EJ, Brent J. Lithium. In: Brent J, Burkhart K, Dargan P, Hatten B, Megarbane B, Palmer R, et al., eds. Critical Care Toxicology. Berlin (DE): Springer; 2017. p. 1-18.
16. Kuczyńska J, Zakrzewska-Sito A. Individualization of lithium therapy based on the monitoring of its level in saliva. Postep Psychiatr Neurol. 2021;30:251-7.
17. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 2018;51:9-62.
18. World Health Organization (WHO). International statistical classification of diseases and related health problems. 11th ed [Internet]. Geneva (CH): WHO; 2019 [updated 2019; cited 2025 Aug 21]. Available from: https://icd.who.int/
19. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59:22-33;quiz 34-57.
20. Amitai M, Zivony A, Kronenberg S, Nagar L, Saar S, Sever J, et al. Short-term effects of lithium on white blood cell counts and on levels of serum thyroid-stimulating hormone and creatinine in adolescent inpatients: a retrospective naturalistic study. J Child Adolesc Psychopharmacol. 2014;24:494-500.
21. Paul R, Minay J, Cardwell C, Fogarty D, Kelly C. Meta-analysis of the effects of lithium usage on serum creatinine levels. J Psychopharmacol. 2010;24:1425-31.
22. Gislason G, Indridason OS, Sigurdsson E, Palsson R. Risk of chronic kidney disease in individuals on lithium therapy in Iceland: a nationwide retrospective cohort study. Lancet Psychiatry. 2024;11:1002-11.
23. Methaneethorn J. Population pharmacokinetic analyses of lithium: a systematic review. Eur J Drug Metab Pharmacokinet. 2018;43:25-34.
24. Reddy DS, Reddy MS. Serum lithium levels: ideal time for sample collection! Are we doing it right? Indian J Psychol Med. 2014;36:346-7.
25. Aps JK, Martens LC. Review: the physiology of saliva and transfer of drugs into saliva. Forensic Sci Int. 2005;150:119-31.
26. Jin ZB, Wu Z, Cui YF, Liu XP, Liang HB, You JY, et al. Population pharmacokinetics and dosing regimen of lithium in Chinese patients with bipolar disorder. Front Pharmacol. 2022;13:913935.