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LETTER TO THE EDITOR

Unexpected fluctuation in serum lithium concentrations during severe mania despite directly observed treatment

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Dear Editor,

Lithium's narrow therapeutic index necessitates close monitoring of serum concentrations. Subtherapeutic levels are usually attributed to non-adherence, inadequate dosing, sampling time, altered renal clearance, or drug interactions (1). Less familiar are unexplained fluctuations occurring during severe mania despite directly observed treatment.

A 20-year-old woman with bipolar disorder and two previous admissions for mania presented with a one-week history of insomnia, pressured speech, aggression, racing thoughts, and excessive spending. Examination revealed elevated mood, marked psychomotor agitation, and erotomanic and persecutory delusions; her Young Mania Rating Scale (YMRS) score was 23. She had no renal, hepatic, cardiac, or thyroid disease and reported no alcohol or substance use. She had previously taken lithium 900 mg/day for six months, which had been reduced to 600 mg/day because of tremor without toxicity. She had discontinued all medication six months before admission; Table 1 therefore reflects titration from zero. Thyroid function was normal on admission (thyroid-stimulating hormone [TSH] 0.83 mIU/L; free thyroxine [fT4] 0.93 ng/dL), and the pregnancy test was negative. By week 4, TSH had risen to 5.2 mIU/L and fT4 had fallen to 0.76 ng/dL; these changes were monitored as possible early lithium-associated thyroid dysfunction.

The course is summarized in Table 1. All lithium measurements were obtained 12 hours after the last dose, at least five days after a dose change, and analyzed in the same laboratory; they therefore reflect steady-state trough concentrations. As the dose increased from 600 to 1200 mg/day, the serum concentration rose from 0.49 to 0.85 mEq/L, yet the concentration-to-dose (C/D) ratio declined progressively (0.82, 0.72, and 0.71). In week 4, despite an unchanged dose, the concentration fell to 0.38 mEq/L as the YMRS score rose to 36 (C/D ratio 0.32). Two samples obtained that day yielded concentrations of 0.40 and 0.38 mEq/L, indicating that the finding was not based on a single measurement. Medication administration under direct observation was confirmed, and a repeat sample three days later, with the dose unchanged, showed a concentration of 0.68 mEq/L (C/D ratio 0.57). She consumed no caffeinated beverages at any point, and caffeine withdrawal would, in any case, be expected to increase rather than decrease medication concentrations (2). There was no vomiting, diarrhea, polyuria, or fever. Agitation subsided after week 6, the YMRS score fell to 16 by week 9, and she was discharged in week 10.

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Table 1: Weekly course of lithium and valproate treatment, serum concentrations, lithium concentration-to-dose ratio, serum sodium, renal and hematological indices, Young Mania Rating Scale (YMRS) score, and treatment changes during admission

W	Lithium dose (mg/day)	Serum lithium (mEq/L)	C/D ratio (mEq/L)/ (g/day)	Valproate dose (mg/day)	Serum valproate (µg/mL)	Sodium (mmol/L)	Creatinine (mg/dL)	eGFR*	Hb (g/dL)	YMRS	Treatment changes
1	600	0.49	0.82	–	–	141	0.78	111	13.1	23	Lithium 600 mg/day, olanzapine 5 mg/day, clonazepam 1 mg/day; quetiapine 25 mg added; lithium increased to 900 mg/day
2	900	0.65	0.72	–	–	137	0.73	121	13.6	25	Lithium increased to 1200 mg/day
3	1200	0.85	0.71	500	NM	138	0.62	131	12.9	NM	Olanzapine increased to 20 mg/day and quetiapine to 100 mg/day; valproate 500 mg/day initiated
4	1200	0.38 → 0.68[b]	0.32 → 0.57[b]	500 → 1000	31.5	140	0.68	128	13.3	36	Dose initially unchanged; regular medication intake confirmed under direct observation; lithium increased to 1500 mg/day at the end of the week
5	1500	0.80	0.53	1000	66.3	NM	NM	NM	NM	34	Clonazepam increased to 3 mg/day
6	1500	0.73	0.49	1000	84.5	141	0.72	123	12.7	38	Lithium increased to 1800 mg/day; propranolol added for tremor
7	1800	NM	–	1000	NM	139	0.78	111	12.9	20	Psychomotor agitation decreased; clonazepam reduced to 1 mg/day
8	1800 → 1500	1.21	0.67	1000 → 2000	78.4	139	0.83	103	12.3	20	Lithium reduced because of the elevated serum concentration; valproate increased to 2000 mg/day
9	1500	0.90	0.60	2000	92.5	138	0.75	117	12.7	16	Clonazepam discontinued
10	1500	1.02	0.68	2000	79.5	139	0.75	117	12.7	NM[c]	Patient discharged

W: Week; C/D: Concentration-to-dose ratio (serum lithium concentration in mEq/L divided by daily lithium dose in g); Hb: Hemoglobin; NM: Not measured. *eGFR is expressed in mL/min/1.73 m^2. All lithium measurements were obtained 12 hours after the last dose and at least five days after a dose change. [b]Initial measurement in week 4 and repeat measurement three days later, with the dose unchanged. [c]The final YMRS assessment was performed in week 9 and was not repeated during the week of discharge.

Two points are noteworthy. First, estimated glomerular filtration rate (eGFR) increased from 111 mL/min/1.73 m^2 on admission to 131 mL/min/1.73 m^2 by week 3, while the C/D ratio declined from 0.82 to 0.71, which may reflect increased renal elimination. However, creatinine-based eGFR is only an indirect marker of true glomerular filtration rate (GFR) and lithium clearance, and lithium undergoes extensive tubular reabsorption; the change in eGFR therefore cannot quantitatively account for the decline. Hemoglobin remained between 12.3 and 13.6 g/dL, arguing against clinically meaningful hemodilution (3, 4). Second, the abrupt fall in week 4, when eGFR was unchanged, cannot readily be explained by renal function. At the height of the episode (weeks 4–6; YMRS 34–38), the mean C/D ratio was 0.45 when calculated using the initial week 4 value and 0.53 when using the repeat value, both lower than the mean of 0.65 during recovery (weeks 8–10), although this comparison depends on the interpretation of the 0.38 mEq/L result. Rittmannsberger and Malsiner-Walli (5) described comparable mood-dependent changes during stable dosing. One proposed explanation is redistribution of lithium into the intracellular compartment during acute mania; plasma and erythrocyte concentrations and their ratio have reportedly been associated with clinical state (6), although these were not assessed here. Valproate does not alter lithium pharmacokinetics in healthy volunteers (7), and olanzapine and quetiapine have no established effect on renal lithium clearance. Nevertheless, these concurrent changes preclude attributing clinical improvement to lithium alone.

Several limitations should be acknowledged. Fluid intake and urine output were not formally measured, and, without 24-hour urinary lithium excretion, renal clearance and tubular handling could not be assessed directly. No clinically apparent change in salt intake was recorded. Body weight increased from 64.3 to 80.2 kg, and its possible contribution to the observed changes could not be determined. Serum lithium concentrations reportedly vary across the menstrual cycle (8); the patient remained amenorrhoeic throughout, but because ovulation and gonadal hormone levels were not monitored, a hormonal contribution could not be assessed. Confirmation of the low concentration in two same-day samples reduces, but does not eliminate, the possibility of analytical error. Most importantly, the redistribution hypothesis was not tested directly: neither the erythrocyte-to-plasma lithium ratio (9) nor brain lithium concentration by ^{7}Li magnetic resonance spectroscopy (10) was measured. Both would be valuable measures in future studies.

This case illustrates that serum lithium concentrations may fluctuate substantially during severe mania and that, under directly observed treatment, a single low concentration should not automatically be interpreted as evidence of non-adherence. Serial C/D ratios, interpreted alongside the clinical course and renal indices, may be more informative than isolated concentrations. Lithium doses escalated during an acute episode should also be reassessed during recovery to reduce the risk of subsequent toxicity (1).

Informed Consent: Written informed consent was obtained from the patient for the scientific use and publication of the patient information included in this case report.

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