https://doi.org/10.15360/1813-9779-2023-1-2307

Achieving and Maintaining Effective Plasma Concentration of Lithium After Oral Administration

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For citation: *Dmitry G. Makarevich, Oleg A. Grebenchikov, Mikhail Ya. Yadgarov, Levan B. Berikashvili, Kristina K. Kadantseva, Valery V. Likhvantsev.* Achieving and Maintaining Effective Plasma Concentration of Lithium After Oral Administration. *Obshchaya Reanimatologiya = General Reanimatology.* 2023; 19 (1): 27–33. https://doi.org/10.15360/1813-9779-2023-1-2307 [In Russ. and Engl.]

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Summary

The aim of the study. To study the achievability and contingency to maintain an effective plasma lithium concentration in the perioperative period in patients undergoing carotid endarterectomy (CEAE) with oral intake of lithium carbonate pills.

Materials and methods. It was a prospective study, as a preparatory stage of the multicenter «BINOS» (NCT05126238) RCT. The sample included 15 patients undergoing elective CEAE. In the course of this study, patients were administered oral lithium carbonate, 900 mg per day during 4 perioperative days: two days before the procedure, in the day of surgery and in the 1st postoperative day. Plasma lithium concentration was monitored every 24 hours during all 4 days from the onset of treatment.

Results. Increased plasma lithium concentrations were found in blood samples taken at 48 hours (0.68 mmol/l [0.53–0.84], $P = 0.004$) and 72 hours (0.68 mmol/l [0.62–0.90], $P < 0.001$), as compared with the initial values (0.14 mmol/l [0.11–0.17]).While during the period between 48 and 72 hours from the onset of treatment the plasma lithium concentration remained in the therapeutic range (0.4–1.2 mmol/l) in 100% of patients.

Conclusion. Oral intake of lithium carbonate pills at a dose of 900 mg/day during 2 preoperative days provided an effective and safe plasma lithium concentration in 100% of patients enrolled in the study.

Keywords: carotid endarterectomy; lithium; pharmacokinetics; drug administration regimen; plasma lithium concentration

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Approximately 10.3 million cases of cerebral infarction (CI) are reported worldwide each year, with ischemic CI accounting for about 80% [1, 2]. In Russia, more than 450,000 cases of stroke are reported annually, and the 30-day mortality rate exceeds 25%. In the following 12 months, about half of the remaining patients die, which is more than 200,000 people [3]. Stroke sequelae are the leading cause of disability [4].

The main cause of most strokes is atherosclerosis with predominant lesions in the carotid arteries [2]. In this context, carotid endarterectomy is considered by current guidelines as the main method for the prevention and treatment of CI [5, 6]. However, despite improved diagnostic methods and techniques of carotid surgery, perioperative cerebral ischemic stroke remains a significant challenge. The incidence of major ischemic stroke after carotid endarterectomy (CEAE) is reported to be 2–2.5%, while the rate of major adverse cardiovascular and cerebrovascular events (MACCE) (composite outcome including death, myocardial infarction, and acute cerebrovascular accident) reaches 5–7% [7, 8].

Neurocognitive disorders manifesting as postoperative delirium or cognitive dysfunction are another serious problem of the postoperative period [9, 10]. In some cases, postoperative delirium is the earliest and sometimes the only manifestation of latent CI [11]. The consequences of postoperative delirium and POCD are not as benign as they may have seemed until recently. Postoperative delirium is associated with a twofold increase in mortality and prolonged ICU and hospital stay [12], while POCD requires prolonged medical and social rehabilitation [13].

Lithium salts have been used in psychiatry for more than 50 years and remain the «gold standard» in the treatment of bipolar disorder [14–16]. However, only recently have researchers drawn attention to a reduced risk of stroke in patients with bipolar disorder taking lithium compared with patients treated with modern antidepressants, antipsychotics, and anticonvulsants [17]. This observation was supported by the results of two independent RCTs showing faster recovery from stroke in patients treated with lithium compared with placebo [18, 19]. In both studies, the target blood concentration of lithium ions was 0.4–0.8 mmol/L [18, 19]. However, there is currently no consensus on the therapeutic concentration of lithium preparations in blood plasma. Thus, a literature review aimed at identifying the therapeutic concentration of lithium ions concluded that the most acceptable range is 0.4–1.2 mmol/L [20]. In the German guidelines, the therapeutic range is also 0.4 to 1.2 mmol/L [21]. At the same time, in the Canadian recommendations, the therapeutic concentration is 0.8–1.2 mmol/L, but the lower limit of this range is reduced to 0.4 mmol/L in elderly patients [22].

Wider use of lithium salts, particularly in anesthesia (for stroke prevention in CEAE) and intensive care (for stroke treatment), is hampered by the lack of a soluble form of the drug. However, achieving and maintaining an effective concentration of lithium salts in the blood using a tablet form of the drug in an acute situation, although quite challenging, is not impossible based on theoretical assumptions. At least, such a possibility has never been investigated.

The aim of this study was to investigate the possibility of achieving and maintaining an effective concentration of lithium ions in the blood of patients in the perioperative period when performing CEAE using a per os preparation containing lithium carbonate.

Material and Methods

This was a preliminary study of the multicenter RCT «BINOS» (NCT05126238). The study was approved by the Ethics Committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (protocol 3/21/6, dated June 27, 2021).

Inclusion criteria were age 18 years and older, signed informed consent, prescription of Sedalit® (lithium carbonate) by the medical team.

Exclusion criteria were known allergy to lithium preparations, neuromuscular diseases specified in the ICD-11, epilepsy, history of leukemia, glomerular filtration rate less than 30 mL/min/1.73 m^2, left ventricular ejection fraction less than 30%, chronic heart failure NYHA class 3–4, known pregnancy at the time of enrollment.

The primary endpoint of the study was the patients' blood lithium salt concentrations on the day of surgery and the day after surgery.

Consecutively, 15 patients who were admitted to the inpatient department of City Clinical Hospital No. 68 for elective CEAE and who met the eligibility criteria were offered to participate in the study. Patients who signed the informed consent and were approved by the medical team were offered initial blood sampling, followed by prescription of Sedalit 300 mg three times a day (total daily dose was 900 mg) two days before the date of surgery. The drug was continued in the postoperative period immediately after the permission to eat solid food on the day of surgery and the first postoperative day.

To study the concentration of lithium ions in the blood, a blood sample of 6.0 ml was taken from an upper extremity vein in the morning before the next dose of Sedalit. Each blood tube was centrifuged, and 2.0 mL of plasma was collected from each blood sample for analysis of lithium ion concentration. Blood samples were collected at 5 time points for each patient: 1 — period between the patient's enrollment in the study and the start of Sedalit, 2 — 24 hours after the start of Sedalit, 3 — 48 hours after the start of Sedalit, 4 — 72 hours after the start of Sedalit, 5 — 96 hours after the start of Sedalit. Time point 1 reflected the initial concentration of lithium ions in the patients' blood, while the other points indicated the accumulation of lithium ions in the patients' blood while taking Sedalit. Time point 3 also reflected the blood level of lithium ions prior to surgery.

Plasma lithium concentrations were determined using an AVL 9180 electrolyte analyzer from Roche Diagnostics at the Moscow Research Institute, a branch of the Serbsky National Medical Research Center for Psychiatry and Narcology of the Ministry of Health of the Russian Federation.

Data analysis was performed according to the «as treated» principle. Thus, if a patient stopped taking Sedalit, subsequent blood test results were excluded from the statistical analysis, as they did not reflect the process of lithium ion accumulation in the blood.

Data distribution was assessed using the Shapiro–Wilk criterion. Quantitative data were presented as medians and interquartile ranges with 5^{th}, 10^{th}, and 90^{th} percentiles; frequencies were presented as percentages. To assess the significance of differences over time, Friedman's rank dispersion analysis was used for paired samples, and Nemenyi's post hoc test was used for multiple comparisons. Box plots were used to visualize the data. All statistical tests were performed using the IBM SPSS Statistics 26.0 software package. Tableau Desktop Software 2019.1 was used for visualization. The significance level was set at 0.05.

Results

A total of 15 patients were included in the study (Fig. 1). The mean age was 57.5 (66; 81) years, and 7 (46.7%) patients were female.

The patients included in the study had a history of comorbidities and were taking medications, as shown in Table 1.

During the study, one patient refused to take Sedalit 24 hours after the start of the study for reasons unrelated to the side effects of the lithium drug. Another patient had hemolysis of a blood sample on day 3 (point 4 — 72 hours) during centrifugation, which prevented evaluation of the lithium concentration in his sample.

The changes in the concentration of lithium ions in the blood of the patients are shown in Table 2.

The changes over time were significant ($P < 0.001$) according to Friedman's non-parametric criterion. The results of a posthoc test showed that the patients had higher blood lithium concentrations on day 2 (0.68 [0.53–0.84] vs. 0.14 [0.11–0.17], $P = 0.004$), day 3 (0.68 [0.62–0.90] vs. 0.14 [0.11–0.17], $P < 0.001$), and day 4 (0.79 [0.67–1.15] vs. 0.14 [0.11–0.17], $P < 0.001$) compared to baseline (Tables 2, 3). In addition, the increase in lithium ion concentration was significant on days 3 ($P = 0.043$) and 4 ($P = 0.002$) compared with day 1 (Table 3).

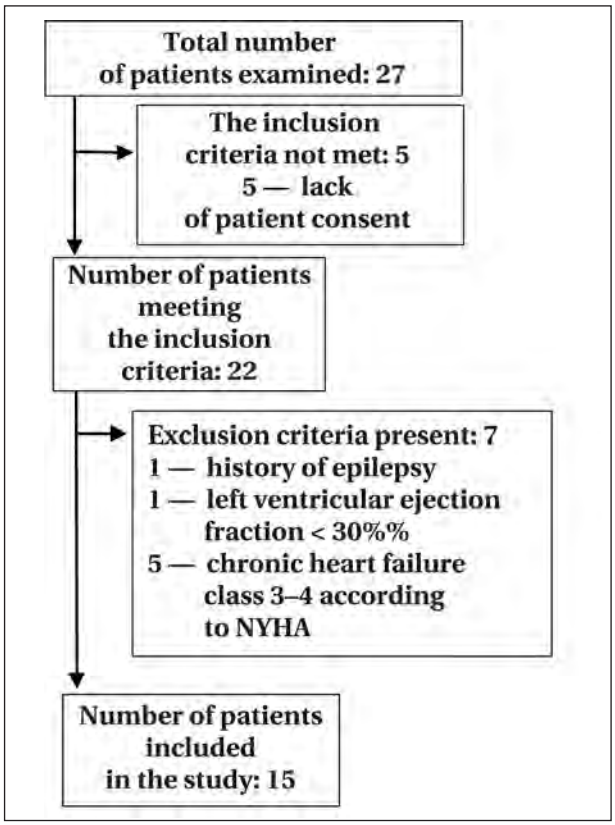

Fig. 1. Flowchart illustrating the process for enrolling patients into the study.

Table 1. Frequency of comorbidities and medications used by patients.

Chronic comorbidities		Medications	
Condition	**Number of patients, *N* (%)**	**Group**	**Number of patients, *N* (%)**
Coronary heart disease	1 (6.67)	β-blockers	4 (26.67)
Myocardial infarction	3 (20.00)	ACE inhibitors	2 (13.33)
Stroke	2 (13.33)	ARBs	6 (40)
Stable angina	2 (13.33)	Calcium channel blockers	2 (13.33)
Atrial fibrillation	1 (6.67)	Antiplatelet drugs	1 (6.67)
Chronic heart failure	2 (13.33)	Anticoagulants	1 (6.67)
Hypertension	13 (86.67)	Statins	5 (33.33)
Diabetes mellitus	5 (33.33)	Antiarrhythmic drugs	1 (6.67)
Bronchial asthma	1 (6.67)	Diuretics	1 (6.67)
Chronic obstructive pulmonary disease	1 (6.67)	Insulin	1 (6.67)
Chronic kidney disease	2 (13.33)	Other hypoglycemic drugs	4 (26.67)
		α-blockers	1 (6.67)
		Neuroprotectors	2 (13.33)

Note. ACE — angiotensin-converting enzyme; ARBs — angiotensin receptor blockers.

Table 2. Concentrations of lithium ions in the blood of patients at different time points.

Parameter	Baseline	Days			
		1	2	3	4
N	15	15	14	13	14
Median (mmol/L)	0.14	0.49	0.68	0.68	0.79
Minimum (mmol/L)	0.00	0.31	0.47	0.55	0.55
Maximum (mmol/L)	0.19	0.81	0.94	1.10	1.77
Percentile					
5	0.00	00.31	0.47	0.55	0.55
10	0.00	00.36	0.48	0.57	0.57
25	0.11	00.45	0.53	0.62	0.67
50	0.14	00.49	0.68	0.68	0.79
75	0.17	00.61	0.84	0.90	1.15
90	0.19	00.73	0.91	1.08	1.66

Table 3. Pairwise comparisons of patients' lithium concentrations at different time points (Nemenyi's posthoc test).

Pairwise comparison	Coefficient	*P-value*
Baseline — Day 1	1.231	0.472
Baseline — Day 2	2.192	0.004*
Baseline — Day 3	3.000	< 0.001*
Baseline — Day 4	–3.577	< 0.001*
Day 1 — Day 2	–0.962	1.000
Day 1 — Day 3	–1.769	0.043*
Day 1 — Day 4	–2.346	0.002*
Day 2 — Day 3	–0.808	1.000
Day 2 — Day 4	–1.385	0.256
Day 3 — Day 4	–0.577	1.000

Note. * — differences are significant.

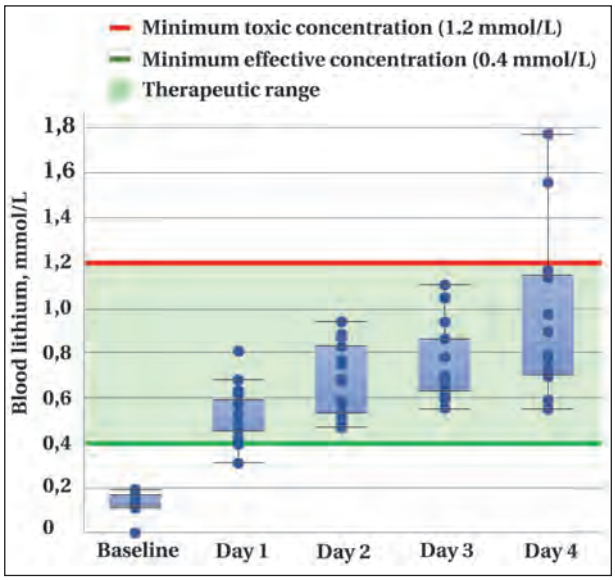

Fig. 2. Changes in the concentration of lithium ions in the blood of patients at different stages of the study (box plot).

Figure 2 shows the changes in lithium ion concentrations in patients' blood at various time points, indicating the minimum effective concentration (0.4 mmol/L), the minimum toxic concentration (1.2 mmol/L), and the therapeutic range (0.4–1.2 mmol/L).

Table 4 compares the percentages of patients relative to the minimum effective and minimum toxic concentrations of lithium ions in the blood.

According to the results of the analysis, the optimal period in terms of pharmacokinetics is 2–3 days (48–72 hours) after starting Sedalit 300 mg 3 times a day, because 100% of patients had lithium concentration values within the therapeutic range, and none of them had values below the minimum effective concentration (0.4 mmol/L) or above the minimum toxic concentration (1.2 mmol/L).

Discussion

A recent study by O. V. Forlenza et al. showed that long-term lithium administration for 2 years at doses ranging from 150 mg to 600 mg per day and reaching plasma concentrations (0.25–0.5 mmol/L) attenuated cognitive and functional impairment in elderly patients with moderate cognitive impairment in the memory domain, which is associated with high risk of Alzheimer's disease.

In the study by S. E. Mohammadianinejad et al., the target plasma lithium ion concentration was 0.4–0.8 mmol/L. It is important to note that the upper limit was considered to be 1.2 mmol/L, which served as a criterion for post-randomization exclusion in this study. These values of lithium ion concentration in blood plasma fully correlate with the limits used in our study.

The lithium drug regimen (300 mg lithium carbonate twice daily) in the study by S. E. Mohammadianinejad et al. differs from that in our study. The lower daily dose of the drug was probably the reason why the average plasma concentrations of lithium ions in the study of S. E. Mohammadianinejad et al. were not reached until day 5. The dosing regimen used by S. E. Mohammadianinejad et al. worked well for long-term dosing in patients with cerebral infarction, but it is difficult to use in perioperative medicine because of the very long time required to reach the target concentration. The dosing regimen of our study allows for faster achievement of therapeutic concentration and its maintenance during the perioperative period.

In another study by Y. R. Sun et al., the target plasma concentration of lithium ions was also 0.4–0.8 mmol/L. This paper is important in comparing lithium dosing regimens. Lithium carbonate doses of 300 mg or more per day were shown to correlate with improved cognitive function compared with those of less than 300 mg per day.

The key finding of our study is that 100% of patients achieved target therapeutic concentrations

Table 4. Number and percentage of patients relative to the minimum effective and minimum toxic concentrations of lithium ions in the blood.

Parameter	Baseline, *N* (%)	Day, *N* (%)				Total, *N* (%)
		1	2	3	4	
Concentration of lithium ions in blood, mmol/L						
<0.4	15 (100)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	17 (23.9)
0.4–1.2	0 (0.0)	13 (86.7)	14 (100)	13 (100)	12 (85.7)	52 (73.2)
>1.2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	2 (2.8)
Total	**15**	**15**	**14**	**13**	**14**	**71**

on days two and three on a 900 mg daily dose of lithium carbonate. In addition, not a single patient had a blood lithium concentration below 0.4 mmol/L, which is the minimum effective concentration of the drug according to literature data [20, 21]. In addition, none of the patients reached the minimum toxic concentration specified in the German and Canadian recommendations [21, 22].

Limitations

Overall, the study was conducted according to the principles of good clinical practice and evidence-based medicine. Perhaps the specific pharmacokinetics of Sedalit in patients with renal and cardiac failure should have been studied. However, given the nature of this work as a preliminary study to the main trial and the inclusion/exclusion criteria for the main study, the authors considered such detail unnecessary.

The authors restricted the study to 15 patients. This was due to the financial resources of the clinic. Theoretically, the study could have been expanded, but the clear result obtained in 15 patients confirmed the correctness of the authors' original position.

Conclusion

Oral lithium carbonate 900 mg/day administered for 2 preoperative days can help achieve effective and safe blood lithium concentrations in 100% of the patients enrolled.

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Received 28.07.2022
Accepted 20.12.2022