

# SALIVA AND SERUM LITHIUM MONITORING IN HOSPITALIZED PATIENTS AND POSSIBILITY TO REPLACE SERUM TO SALIVA

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## ABSTRACT

The lithium ions concentration in human serum and saliva was determined using dry-slide technology Vitros 250 Analyser (Ortho Clinical Diagnostic) and atomic absorption spectrometry Perkin Elmer 403 (AAS). We analyzed lithium ions in 100 serum and saliva specimens of patients after oral administration of lithium carbonate (3x 300mg) Jadran, Galen Laboratory Rijeka. Saliva and blood were taken 2 and 12 hours after the last dose. At the same time lithium ions at samples of blood and saliva were determined with both methods which showed high level of correlation. The mean difference of lithium ions between saliva and serum was statistically significant for  $p < 0,05$  using t student test. At saliva we got constant of elimination  $Kel = 0,02 \cdot h$  and elimination half life ( $t_{1/2}$ ) was  $t_{1/2} = 34,6$  h. For serum was  $t_{1/2} = 24$  h what means that lithium ions elimination is slower from saliva then from serum. That is the reason why probably concentration at saliva is higher then at serum. Lithium elimination is two compartment pharmacokinetic model where important part of compartment are saliva and salivary glands. At a certain point in medical treatment it could be expected to use controlled determination of lithium ions in saliva with serum as control.

KEY WORDS: lithium, serum, saliva.

## INTRODUCTION

Lithium carbonate was the first modern antimanic agent and has been the pharmacologic mainstay of treatment for patients who have bipolar disorder. The lithium ions is absorbed readily and almost completely from the gastrointestinal tract. Complete absorption occurs in about eight hours, with peak concentrations in plasma occurring two to four hours after an oral dose. Monitoring of lithium in serum twelve hours after the last dose is necessary in medical treatment with lithium preparations. It is a drug with narrow therapeutic range in the serum is 0,6-1,2 mmol/L (1,2). The determination of salivary drug concentrations is one of the major domains for the application of saliva in laboratory medicine. Lithium ions do not build with proteins and determination in saliva is interesting for analytical research. Saliva lithium has been reported as being a useful alternative to monitoring blood levels but accuracy of saliva lithium monitoring has been questioned (3-6). In this study, using samples of serum and saliva after two and twelve hours lithium carbonate last dose we make analysis by the Vitros Analyse 250 dry slide technology and atomic absorption spectrometry Perkin Elmer 403 (AAS) and compared the results. We tried to find possible way of using saliva in therapeutic drug monitoring of lithium treated patients.

## MATERIAL AND METHODS

### DRY SLIDE TECHNOLOGY

The dry slide technology Vitros 250 Analyser (Ortho Clinical Diagnostic) was used for the determination of lithium ions in serum and saliva. As the lithium ion binds to the crown – ether, a shift in the peak absorbance of the chromophore conjugate occurs. The increase in absorbance at 600 nm is proportional to the concentration of lithium in the sample. The intensity of the dye is measured by reflectance spectrophotometry at 2,3 minutes at 37°C (7).

### ATOMIC ABSORPTION SPECTROMETRY

The atomic absorption spectrometry Perkin Elmer 403 (Perkin Elmer) was used for the determination of lithium ions in serum and saliva. Lithium ions determination was made at wave light 670,08 nm. As the light source was used hollow cathode lamp with the cathode made of lithium (8).

### DRUG AND SAMPLE PREPARATION

Lithium carbonate® 300 mg tablets were obtained from Jadran, Galen Laboratory (Rijeka, Croatia). Blood sam-

ples for determination of concentration of lithium ions in serum were obtained at two and twelve hours after drug administration. The samples of blood were collected by serum separator Vacutainer Tubes (Beckton Dickinson, Rutherford, NJ 07070 USA) with 3,5 mL of volume. After rinsing the mouth with water, samples of unstimulated mixed saliva were collected over five minutes at glass vials at the same times blood samples were drawn. Serum samples were obtained by centrifugation at 3000 rpm and saliva at 4000 rpm. The serum and saliva samples were kept frozen at -20 °C prior to analysis.

### PATIENTS

This investigation was done respecting ethical standards stipulated in the Helsinki Declaration and a detailed protocol was approved by the National Ethical Committee of the Ministry of Health of Republic Slovenia. All patients gave written, informed consent. The study completed 10 males and 15 females (age: 20 – 50 years old). All patients were treated with lithium carbonate 3x300 within a period from four months to thirteen years. The patients were hospital treated at the Psychiatric Clinic of the Sarajevo University Clinical Center and the Psychiatric hospital «Jagomir» in Sarajevo.

### PHARMACOKINETIC ANALYSIS AND STATISTIC

The pharmacokinetic analysis was performed with calculation of farmakokinetic parameters constant of elimination (Kel) for saliva and elimination half life ( $t_{1/2}$ ) for saliva and serum. Congruency of results has been investigated by analysis of the linear regression expressed as a coefficient of correlation (r) and student t test for  $p < 0,05$ . Paired samples student t – tests were used to compare serum and saliva lithium ions concentration gave values of  $p < 0,05$  were considered statistically significant.

## RESULTS AND DISCUSSION

In the present study, we made a comparison of lithium ions from 100 blood serum and saliva samplers using dry slide technology and AAS. We took serum and saliva samples 12 and 2 hours after last dose of lithium carbonate. The results of the lithium ions comparison between serum and saliva after 12 hours determined with Vitros Analyser are shown at Figure 1. The correlation between saliva and serum lithium concentrations was highly significant: ( $r=0,8601$ ,  $p < 0,05$ ). The regression equation revealed a slope of 0,373 and a y axis intercept of 0,299. The mean serum lithium level was  $0,572 \pm 0,145$  and mean saliva level was  $0,732 \pm 0,336$  after 12 hours using dry slide

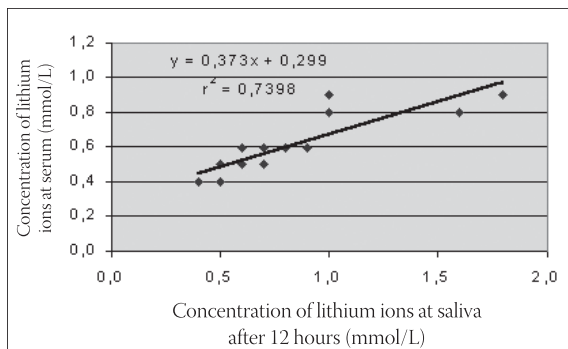


FIGURE 1. Comparison of serum and saliva values of lithium ions (mmol/L) 12 hours after last dose obtained by Vitros analyzer 250 dry slide technology from 25 patients samples.

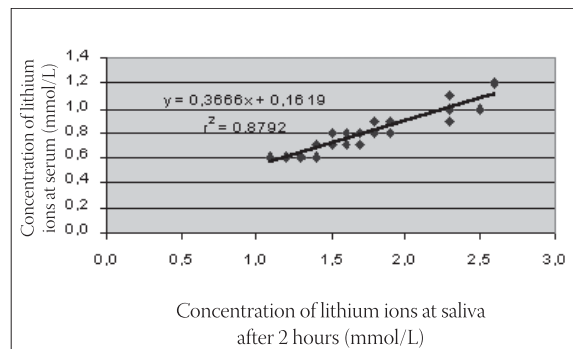


FIGURE 2. Comparison of serum and saliva values of lithium ions (mmol/L) 2 hours after last dose obtained by Vitros analyzer 250 dry slide technology from 25 patients samples.

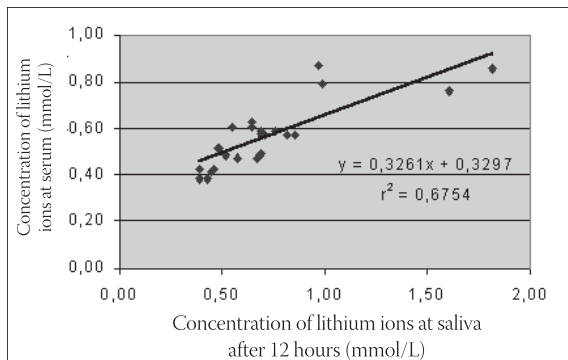


FIGURE 3. Comparison of serum and saliva values of lithium ions (mmol/L) 12 hours after last dose obtained by AAS from 25 patients samples.

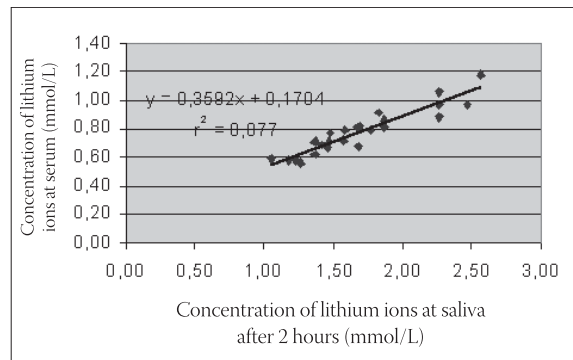


FIGURE 4. Comparison of serum and saliva values of lithium ions (mmol/L) 2 hours after last dose obtained by AAS from 25 patients samples.

technology. The results of the lithium ions comparison between serum and saliva after 2 hours determined with Vitros Analyser are shown at Figure 2. Very good correlation was noted between saliva and serum lithium ions after 2 hours using dry slide technology ( $r = 0,9376$ ,  $p < 0,05$ ). The regression line had slope of 0,3666 and y axis intercept of 0,1619. After two hours mean serum lithium level was  $0,788 \pm 0,161$  and mean saliva level was  $1,708 \pm 0,413$ . A comparison of lithium ions results between saliva and serum after 12 hours determined with AAS are shown at Figure 3. The correlation coefficient was  $r = 0,8218$  and regression line had slope of 0,3261 and y axis intercept of 0,3297. The main difference between the serum and saliva was statistically significant for  $p < 0,05$  using student t test. After 12 hours mean serum lithium level was  $0,562 \pm 0,1373$  and mean saliva level was  $0,712 \pm 0,3462$  using AAS method. The results of the lithium ions comparison between serum and saliva after 2

hours determined with AAS are shown at Figure 4. The regression line had a slope 0,3592 and a y axis intercept of 0,1704 and correlation coefficient was  $r = 0,9364$ . The main difference between serum and saliva was statistically significant for  $p < 0,05$  using student t test. After 2 hours mean serum lithium level was  $0,776 \pm 0,1572$  and mean saliva level was  $1,686 \pm 0,4098$  using AAS method. Many publications reported contradiction results of the relationships between saliva and serum lithium levels. Some have reported good correlations and others low correlations between two body fluids (3-6). The saliva lithium levels were about two to three times greater than serum levels, lithium ions are actively secreted into the saliva. The elimination half life in the present study was estimated for saliva  $t_{1/2} = 34,6$  h and serum  $t_{1/2} = 24$  h. The elimination rate constant by our patients was  $K_{el} = 0,02h^{-1}$ . In previous study of other authors was  $t_{1/2}$  (serum) =  $22 \pm 8$  h;  $t_{1/2}$  (serum) =  $28 \pm 7,9$  h by adult patients. Valules of elimination half

life by children were lower than by adults  $t_{1/2}$  (serum) =  $17,9 \pm 7,4$  h and  $t_{1/2}$  (serum) =  $15,6 \pm 8,2$  h (5,9,10). At other studies the elimination rate constant of lithium by adult patients ranged from  $0,026 \text{ h}^{-1}$  to  $0,1276 \text{ h}^{-1}$  (11). Lithium concentration at saliva are more variable than

serum concentrations and using saliva could be acceptable only with determination lithium ions at serum too (12-14). The present study results have shown that concentration of lithium ions at saliva are increasing and decreasing in dependence of ions concentration at serum.

## CONCLUSION

Our study have found good correlation between serum and saliva at two daily intervals using both method. Concentration of lithium ions at saliva point at some within and between subject variation and for her use we need discovery of these variation. The problem will be solved if we find equation of linear regression for every patient singly. Using saliva for determination lithium concentration at serum is possible by manic – depressive patients at hospital treatment which state is stable. After two hours concentration at saliva are the highest and we find good correlation between saliva and serum. It would be eventually possible that saliva could change blood two hours after last lithium carbonate dose where we got high correlation coefficient. At saliva we got  $Kel = 0,02 \text{ h}^{-1}$  and half life of saliva was  $t_{1/2} = 34,6$  h. For serum half life was  $t_{1/2} = 24$  h what means that lithium ions elimination is slower from saliva than from serum. That is the reason why probably concentration at saliva is higher than at serum. Lithium elimination is present as two compartment pharmacokinetic model. The salivary lithium concentration never decreased to serum level, indicating an active transport of lithium into the saliva. There was no evidence of lithium storage at the salivary glands. Lithium ions concentration at saliva increase and decrease in dependence of serum concentration so, we can talk about reversible transport.

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