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Salivary Lithium Determination : Clinical Relevance and Comparison of Methods of Estimation by Flame Photometry and Atomic Absorption Spectrophotometry

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Abstract

Lithium levels were determined in serum and saliva samples from 26 patients on lithium therapy using flamephotometric and atomic absorption spectrophotometric methods. No significant differences were observed ion comparing the results obtained by these two methods of estimation. Further, the correlation between lithium levels in serum and mixed saliva showed a mean ratio of 1 : 2.25, with an overall correlation coefficient (r) of 0.63 (p <0.001). The relationship using linear regression analysis was described by the equation, y=1.36x + 0.63. Although statistically significant correlation was obtained between serum and mixed saliva lithium concentrations, there was an unacceptably high individual variation of paired results. Serially paired results in individual patients also showed occasional wide variations. The findings from the present study do not support the suggestion that saliva can be safely used as a substitute for serum to monitor lithium therapy.

Key words -
Salivary lithium,
Serum lithium,
Atomic absorption spectrophotometry

In the treatment of manic phase of bipolar affective disorders and in the prophylaxis of recurrent depressions, the use of lithium carbonate is well established [1], [2], [3], [4], [5], [6], [7]. The therapeutic application of the drug has been known since the work of Cade [8]. However, toxic effects of its administration were recognised almost at the same time by Corcoran et al [9]. Since the therapeutic: toxic ratio for lithium is low, regular monitoring of its levels in serum is imperative in patients on lithium therapy. The amount of lithium required to achieve a therapeutic response depends on the concentration of the ion in serum rather than on the actual dosage given per day. Blood levels of lithium, thus, reflect

its distribution throughout the body.

The distribution of lithium between plasma and saliva was first demonstrated by Good [10]. The alternative use of saliva to monitor lithium therapy was first suggested by Shospin et al [11] and Spring and Spirtes [12]. Monitoring of lithium levels in saliva provides certain obvious advantages. It spares the patient frequent venous punctures, besides being economical, eliminating the need for the patient to frequently visit a physician or laboratory to have blood drawn. A number of studies have thus been conducted to determine the validity and efficacy of such determinations. Several investigators have demonstrated high correlation between saliva and serum lithium concentrations and have suggested that saliva determinations can be used for monitoring lithium therapy [13], [14], [15], [16]. However, some other studies have reported wide variations in serum saliva lithium ratios between patients [17], [18], [19]. The present study was taken up to

i) compare the methods of lithium determination in serum and saliva by flame photometry and atomic absorption spectrophotometry; and
ii) to investigate if salivary lithium determinations can replace conventional serum lithium estimations for monitoring lithium therapy.

Material and Methods

Mixed saliva and blood samples were collected from affectively ill patients (n=26) who were on lithium therapy. The samples were collected approximately 12 hours (range 11-14 hrs) following the last dose of lithium in-take. Immediately after collection of about 5 ml of mixed saliva from each patient, blood sample was drawn and serum separated. The saliva samples were subjected to centrifugation to remove particulate matter and mucous, prior to analysis.

The serum and saliva samples were diluted 1:10 and 1:20 respectively with diluent containing 0.1 ml of triton X-100 and 0.112 g of KCl in 1 litre of deionized, double distilled water.

Serum lithium determination:

The lithium carbonate standard solutions (lithium concentration range of 0.1 - 2.0 mEq/L) as well as blank solution used contained sodium (140 mEq/L), calcium (5 mEq/L) and potassium (5mEq/L). The blank and standard solutions were diluted (1:10) with the diluent.

Saliva lithium determination :

The blank solution and the suitable lithium carbonate standard solutions contained sodium and potassium in the concentration range of 30 mEq/L and 20 mEq/L respectively. The blank and the standard solutions were diluted 1:20 with the different prior to analysis.

Instrumentation :

Flameless atomic absorption spectrophotometer (Pye Unicam) with autothermal facilities was used for determining the lithium content in serum and saliva samples. For flame emission photometric estimations, systronics flame photometer (MK Type II) equipped with type 125 digital unit was used. Using suitable standards, the instruments were calibrated each time before use and the samples analysed. The final concentrations were calculated from the calibration graphs.

Results

The range and mean values of lithium concentrations in serum and saliva determined by using flamephotometric and atomic absorption spectrophotometric methods are shown in Tables 1 & 2. A high correlation coefficient (r) of 0.99, as also the comparison using student's t-test, did not indicate any significant difference in the values obtained by the two methods.

Table 1 - Comparison of serum lithium concentration (mEq/L) as determined by the methods of flame photometry and atomic absorption spectrophotometry

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The t-test performed with 95% confidence limits indicated no significant difference in the values obtained using the two methods.

Table 2 - Comparison of salivary lithium concentrations (mEq/L) as determined by the methods of flame photometry and atomic absorption spectrophotometry

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The 't' test performed with 95% confidence limits indicated no significant difference in the values obtained using the two method.

The correlation of serum and mixed salivary lithium levels (measured by flamephotometric method) showed a mean ratio of 1:2.25, with a correlation coefficient (r) of 0.63 ($p<0.001$). The relationship using linear regression analysis was described by the equation, $y=1.36x + 0.63$ (Fig. 1)

.Correlation between serum and saliva lithium level, expressed as mEq/L

Discussion

The present findings lend little support to the suggestion that salivary lithium levels (in contrast to serum levels) can be used as reliable indicators in monitoring lithium therapy. A correlation coefficient of 0.63 though statistically significant, would not indicate a reliable and reproducible correlation so as to render the method feasible for routine clinical application. Moreover, there is an unacceptably high individual variation of paired results. Serially paired results in individual patients also show occasional wide variations. The possibility of methodological limitations contributing to the observed variations, is ruled out since we did not find any significant difference in the lithium concentration values as determined by flame emission photometry and atomic absorption spectrophotometry.

The results from the present study are, thus, in agreement with the findings of Sims and White [17], Sethi et al [18] and Richardson and King [19]. Our observations are however, in disagreement with the reports of highly significant correlation between serum and salivary lithium levels, demonstrated by Neu et al [14], Vershese et al [15] and Preskorn et al [16]. Based on their observations, these investigators have suggested that salivary lithium determinations can safely replace the conventional serum lithium estimations for monitoring the drug therapy.

However, the data reported by Verghese et al [15] show a salivary lithium level of 20 mmol/L to occur corresponding to a wide range of serum lithium levels between 0.6 mmol/L and 1.2 mmol/L. Similar

variations have been observed in the present study as well. Also Richardson and King [19] observed a wide variation of serum : saliva lithium ratio between patients and in the same patient at different times.

Our observations regarding variation of serum: saliva lithium ratio may partly due to the changes in the flow rate of saliva. Difficulty in reproducing the steady state levels of secretion of mixed saliva at different times as such or under the influence of various stimulants have earlier been reported by Selinger et al [20]. To ensure better reproducibility of salivary flow rate, Seliger et al [20]. used critic acid to stimulate maximal flow, the resulting burst of saliva from the parotid duct being collected by means of a modified Teflon-Lashley cup.Lithium levels in the parotid saliva thus collected were reported to be highly correlated with plasma lithium levels ($r=0.98$, $p<0.001$) [20]. Adopting a similar method of parotid saliva collection, Richardson et al [19], however, could not replicate these findings. Further, for routine clinical practice, such an elaborate and delicate procedure of parotid saliva collection may be of little advantages compared to the readily accessible blood collection procedures.

It should be pointed out, however, that the patient population in the present study included those who were being treated with only lithium and also the patients who besides lithium received neuroleptic or tricyclic medication. In view of the well characterised control of ionic and enzymatic secretion of parotid gland by neurotransmitters [21], it is possible that psychotropic drugs may be unpredictably altering the salivary flow rate, thus affecting the results.

Further studies would be required to investigate if salivary lithium monitoring should be clinically feasible, at least, in patients who are on lithium therapy alone, using serum : saliva ratio, calculated for each individual patient, as the monitoring index.

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1.Baastrup P, The use of lithium manic-depressive psychosis
Comprehensive Psychiatry Page: 5: 396-408, 1964
2.Gerhson S, The use of lithium salts in psychiatric disorders
Diseases of Nervous System Page: 29: 51-55, 1968
3.Angst J & Weis P, Lithium prophylaxis in recurrent affective disorders
British Journal of Psychiatry Page: 116: 604-614, 1970
4.Baastrup P, Prophylatic lithium : double blind discontinuation in manic depressive and recurrent depressive disorder
Lancet Page: ii : 326-330, 1970
5.Coppen A, Noguera R, Bailey J, Burns B H, Swani M S, Hare E H, Gardner R & Maggs R, Prophylatic lithium in affective disorders
Lancet Page: ii: 275-279, 1971
6.Hullin R P, McDonald R & Allsopp M N E, Prophylatic lithium in recurrent affective disorders
Lancet Page: i: 1044-1046, 1972
7.Mendels J, Secunda S K & Dyson W L, A controlled study of the antidepressant effects of lithium carbonate
Archives of General Psychiatry Page: 26: 154-157, 1972

8.Cade J R, Lithium salts in the treatment of psychotic excitement
Med. J. Aust Page: 36: 349-352, 1949
9.Corcoran A C, Taylor R D & Page I H, Lthium poisoning from the use of salt substitutions
JAMA Page: 139: 685-688, 1949
10.Good C A, An experimental study of lithium
American Journal of Medical Sciences Page: 125: 273-284, 1903
11.Shopsin B, Gershon S & Pickney L, The secretion of lithium in human mixed saliva : effects of ingested lithium on electrolyte distribution in saliva and serum
Intl. Pharmacopsychiat Page: 2:148-169, 1969
12.Spring K R & Spirtes M A, Salivary excertion of lithium: human parotid and submaxillary secretions
Journal of Dental Research Page: 48: 546-549, 1969
13.Sims A C P & White A C, Saliva and serum lithium estimations in psychiatric patients
British Journal of Psychiatry Page: 124: 106-107, 1974
14.Neu C, Dimascio A & William D, Saliva lithium levels : Clinical applications
Appl. Psychiat Page: 132: 66-68, 1975
15.Verghese A, Indrani M, Kurivilla K & Hill P G, Usefulness of saliva lithium estimation
British Journal of Psychiatry Page: 130: 148-150, 1977
16.Prekorn S H, Abernethy D R & Mcknelly W V, Use of saliva lithium determination for monitoring lithium therapy
Journal of Clinical Psychiatry Page: 39: 756-758, 1978
17.Sims A, White A C & Garvey K, Problems associated with the analysis and interpretation of saliva lithium
British Journal of Psychiatry Page: 132: 152-154, 1978
18.Sethi N, Prakash R & Sethi B B, Relationship between lithium levels of saliva and serum
Biological Psychiatry Page: 16: 413-414, 1981
19.Richardson R E & King J R, Salivary lithium : a trial of Selinger's method in Sri Lanka
British Journal of Psychiatry Page: 19: 1129-1132, 1984
20.Selinger D, Hailer A W, Nurnberger J J, Simmons S & Gerhson E S, A new method for the use of salivary lithium concentrations as an indicator of plasma lithium levels
Biological Psychiatry Page: 17: 99-102, 1982
21.Mangos J A, Characterisation of autonomic receptors in isolated human paraccinar cells
J. Dent. Res Page: 59: 168, 1980