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Study of lithium concentration in saliva and plasma of Bipolar (mania) patients hospitalized at psychiatric ward of Ahwaz Golestan Hospital (Iran)

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ABSTRACT

Lithium treatment is used to treat mania in bipolar disorder. Since taking blood samples from such patients are difficult, in this research for the first time in Iran, we decided to measure the concentration of lithium in other biological fluids such as saliva, as an alternative method for measuring lithium in blood samples. Lithium concentrations after 8-12 hours of the last oral doses in saliva and plasma of 33 manic patients hospitalized at Ahwaz Golestan Hospital (in Iran) under long-term lithium therapy were measured. Samples of saliva or blood were collected. The lithium concentrations of the samples were measured by using flame emission (photometry) technique. The mean blood lithium concentration was found to be (0.97±0.04) and the mean saliva lithium concentration was (2.22±0.06). On the basis of the results obtained in this research and on the basis of statistical calculations, the following equation was obtained: $[Li]_p=0.362[Li]_s+0.166$, where $[Li]_s$=saliva lithium concentration and $[Li]_p$=plasma lithium concentration. On the basis of this equation, salivary lithium concentration is always higher than plasma lithium concentration and the ratio between them is 2.29 and the correlation coefficient is 0.58 ($P<0.01$). The results obtained in this research demonstrate the possibility of using salivary lithium measurement for monitoring patients on prolonged therapy. Such method may help clinical laboratories to improve the TOM of lithium.

Key words: Mania, depression, bipolar, lithium, lithium carbonate, saliva, plasma.

INTRODUCTION

Manic Depressive Psychosis is an illness marked by severe and often dramatic mood swings. These consist usually of periods of mania, which fluctuate with periods of depression and periods of stability during which the sufferer often behaves and reacts in a perfectly normal manner.[1] A manic episode, or **mania**, is when a person experiences several of the symptoms presented in (table 1) at the same time. A depressive episode, or **depression**, is when a person experiences several of the symptoms presented in (table 1) at the same time. Bipolar disorder is an illness which exposes people to these mood changes over the course of time. Lithium is used to even out the **highs (mania) and lows (depression)** in mood associated with of bipolar disorder. Manic Depression is thought to be caused by chemical imbalances in certain brain cells responsible for emotions and behaviour. In some cases, lithium is used to treat people with depression even though they have never experienced a manic episode. Lithium acts to correct these imbalances and therefore stabilise sufferers' moods. In doing so, Lithium causes little, if any, interference with mental or physical capacity and sufferers continue to have normal emotional reactions. For this reason, it is often better tolerated by the body than other medications used to treat manic depression.[1] **Lithium** in pharmacology refers to the lithium ion, Li^+, used as a drug. Lithium is administered in a number of chemical salts of lithium, which are used primarily in the treatment of bipolar disorder as mood stabilizing drugs. In bipolar disorder they have a role in the treatment of depression and mania acutely and in the long term. As a mood stabiliser, lithium is probably more effective in preventing mania than depression, and may reduce the risk of suicide. In depression alone (unipolar disorder) lithium can be used to augment

other antidepressants. Upon ingestion Lithium becomes widely distributed in the central nervous system and interacts with a number of neurotransmitters and receptors, decreasing noradrenaline release and increasing serotonin synthesis.[2] Lithium has also been used to treat people with **schizophrenia** in cases where changes in thinking happen at the same time as a mood change that looks like either mania or depression Bipolar disorder requires long-term treatment.[1] Lithium is used for the treatment of manic/ depressive (bipolar) and depressive disorders. It interferes at several places inside cells and on the cell surface with other positively charged atoms such as sodium, potassium, calcium, and magnesium which are important in many cellular functions. Lithium interferes with the synthesis and reuptake of chemical messengers by which nerves communicate with each other (neurotransmitters). Lithium also affects the concentrations of tryptophan and serotonin in the brain. In addition, lithium increases the production of white blood cells in the bone marrow. Lithium's effects usually begin within one week of starting treatment, and the full effect is seen by 2 to 3 weeks. Lithium has been used since the 1950's. The currently most frequently used preparation, lithium carbonate, was not approved by the FDA until 1970.[1]Today it remains a commonly used medication for this illness. The amount of lithium in the blood can be measured. Studies have generally shown that blood levels between 0.6–1.2 (mmol/L) give patients the best chance of response to lithium. Lithium may be prescribed by itself or along with other medications to help manage your Bipolar mood symptoms.[2]Common side effects of lithium include nausea, loss of appetite, and mild diarrhea. These side effects will usually go away after the first few weeks as your body adjusts to the medication. Dizziness and hand tremors have also been reported. Increased production of urine and excessive thirst are two common side effects that are usually not serious problems. Other side effects of lithium include weight gain, hypothyroidism (low levels of thyroid hormone), increased white blood cell count, acne, and skin rashes. Signs of hypothyroidism include dry skin, hair loss, sensetivity to cold, hoarseness, mental depression, and weight gain. The precise mechanism of action of Li^+ as a mood-stabilizing agent is currently unknown. It is possible that Li^+ produces its effects by interacting with the transport of monovalent or divalent cations in neurons. An increasing number of scientists have come to the conclusion that the excitatory neurotransmitter glutamate is the key factor in understanding how lithium works. The required dosage (15-20mg per kg of body weight) is slightly less than the toxic level. Lithium toxicity is compounded by sodium depletion. In long-term use, therapeutic concentrations of lithium have been thought to cause histological and functional changes in kidney.[2]

EXPERIMENTAL

All the measurements were made by using a Clinical Flame Photometer (Corning 405C, England). The standard samples used were 2mL Multical™ vials, each contained Na (140 meq/L), K (5 meq/L), Li (1.5 meq/L), Cl (100 meq/L), and Ca (2.5 meq/L) which were only used for laboratory

Table - 1: Some of the more common symptoms of mania and depression

No.	Common symptoms of Mania	No.	Common symptoms of depression
1	Inability or unwillingness to sleep	1	Lack of energy
2	Irritability and impatience	2	Lack of concentration
3	Constant flow of ideas	3	Decreased interest in life
4	Constant wish to talk	4	Anxiety and lack of concentration
5	Loss of judgement	5	Apathy and suicidal thoughts
6	Impulsive badly thought out decisions	6	Loss of sexual interest
7	Euphoria or out of place sexual interest (Advanced symptoms include hallucination and loss of contact with reality)	7	Inability to concentrate
8		8	Loss of appetite and weight

analysis. Analysis of plasma lithium was done in the hospital clinical laboratory with routine clinical samples using flame emission photometry. Saliva samples were also analyzed by flame emission photometry. The population studied consisted of 33 manic-depressive patients of the psychiatric ward at Ahwaz Golestan Hospital of Iran. All patients were women aged from 19 to 54 years and were treated from the early to the end of winter 2001 with lithium carbonate. They received from 900 mg to 1500 mg lithium carbonate in several doses per day. All of the patients were being treated with other drugs as well (Table 2). 33 patients were followed for about 3 months and serial blood and saliva samples were drawn (3 samples per subject). Whole saliva was collected from the patients. The patients were instructed to accumulate saliva in their mouth and spit into a labeled and capped polyethylene vessel. The salivary and blood samples were centrifuged and diluted with deionized water. The results were analyzed statistically by standard techniques of determination of correlation coefficients and Student's test of significance.

Collection and storing blood samples

For performining each experiment, 2.5-3 mL of the patient's blood was needed in order to obtain 1.5 mL serum from it. Blood samples were taken from the arms of the patients by using 5 mL disposable syringes after 8-12 hours from the last lithium carbonate dosage. The blood samples were immediately transferred into labeled Pyrex test tubes. The clots of the blood inside the tubes were separated by using a wooden applicator, then, the tubes were centrifuged with 1500 rpm for 20 minutes. The yellow upper layers (serums) were separated and transferred into labeled polyethylene tubes and stored in a refrigerator.

Collection and storing Saliva samples

For performining each experiment, 3 -4 mL of the patient's saliva, after 8-12 hours from the last lithium carbonate dosage, was needed. The samples were collected in labeled polyethylene capped vessels.

Preparation of standard solutions

For the calibration of the flame emission photometer and drawing the standard curves, we used the standard 2mL Multical™ sample which contained Na (140 meq/L), K (5 meq/L), Li (1.5 meq/L), Cl (100 meq/L), and Ca (2.5 meq/L). Standard solutions were made by taking the appropriate amount of the standard Multical™then diluted with deionized water (Table 3). These standard solutions were used for drawing the standard curves.

Measurement of the emission of the standard solutions and the samples

The emission and concentration (mmol/L) of each of the standard solutions were measured

Table - 2: Psychotropic Drugs used by patients in addition to Li_2CO_3

No.	Patients treated with:	No. of patients
1	Biperidone	17
2	Perphenazine	14
3	Amitriptyline	1
4	Trifluoperazine	5
5	Chlorpromazine	4
6	Clonazepam	16
7	Sodium Valproate	4
8	Cyproheptadine	3
9	*Thioridazine*	*2*

Table - 3: Preparation of the standard solutions

Volume taken from the standard Multical™ sample mL	Final volume (mL)	Concentration (mmol/L)
1	1	1.5
0.67	1	1
0.53	1	0.8
0.40	1	0.6
0.33	1	0.5
0.27	1	0.4
0.13	1	0.2

by using the flame photometer (Table 3), then the concentration of each of the serum and saliva samples were measured (Table 4). Deionized water was used as blank.

Table - 4: Salivary and serum lithium concentrations (mmol/L) of patients hospitalized at Ahwaz Golestan Hospital (Iran)

Patient No.	Serum conc.	Saliva conc.	Patient No.	Serum conc.	Saliva conc.	Patient No.	Serum conc.	Saliva conc.
1	1	2.7	12	0.9	2.6	23	1	2.4
2	0.5	1.3	13	0.8	2.3	24	0.9	1.7
3	0.9	1.9	14	0.8	2.7	25	1.1	1.9
4	0.9	2.1	15	1.4	2.8	26	1	1.8
5	0.8	2.1	16	0.8	2.1	27	1.1	2.6
6	0.8	1.7	17	1	2.4	28	0.7	1.8
7	0.7	2.3	18	1.7	2.9	29	0.8	2.1
8	1.1	2.4	19	1.1	2.3	30	1.1	2.6
9	1.4	2.3	20	0.9	2.2	31	0.9	2.4
10	0.9	2.3	21	0.8	2.1	32	1	1.8
11	1.1	2.4	22	1	1.9	33	1.1	2.3

DISCUSSION

Lithium treatment is used to treat mania in bipolar disorder. In order to determine the lithium carbonate (Li_2CO_3) doses used for the treatment of manic patients usually, after taking this drug, its concentration in blood samples are measured. Since taking blood samples from such patients are difficult, therefore, one of the main purposes of this research was to study the possibility of using salivary lithium concentration for lithium monitoring of psychiatric patients hospitalized at Ahwaz Golestan Hospital (Iran) for the first time in Iran, as an alternative method for measuring lithium in blood samples of the patients. Another purpose was to check the constancy of the ratio between salivary and plasma concentrations of lithium at various times after oral doses in the hospitalized patients under lithium treatment. Lithium concentrations in saliva and plasma were measured in 33 hospitalized patients under long-term lithium therapy every week (after 8-12 hours of the last oral doses) in the morning. Samples of saliva or blood were collected. The lithium concentrations of the samples were measured by using flame emission (photometry) technique. The minimum and maximum serum and salivary Li concentrations at successive weeks were measured and presented in Tables 5 and 6,

Table - 5: Minimum and Maximum Serum Li concentration in each week

Week No.	No. of Patients	Minimum serum Li conc. (mmol/L)	Maximum serum Li conc. (mmol/L)
1	2	0.50	1.00
2	6	0.70	1.10
3	2	0.90	1.40
4	3	0.80	1.10
5	6	0.80	1.70
6	8	0.80	1.10
7	6	0.70	1.10
Total	33		

Table - 6: Minimum and Maximum Salivary Li concentration in each week

Week No.	No. of Patients	Minimum salivary Li conc. (mmol/L)	Maximum salivary Li conc. (mmol/L)
1	2	1.30	2.70
2	6	1.70	2.40
3	2	2.30	2.30
4	3	2.30	2.60
5	6	2.10	2.90
6	8	1.70	2.60
7	6	1.80	2.60
Total	33		

respectively. Also, the amount of serum and salivary Li of the patients under investigation were determined and presented in Table 7. A comparison was made between the serum and salivary Li concentrations at successive weeks and presented in Tables 7 and figure 1. The salivary and serum

Table - 7: The mean Li (mean±se) in salivary and serum of the Bipolar patients at Ahwaz Golestan Hospital, Iran.

Week No.	No. of Patients	Serum Li conc. (mmol/L)	Salivary Li conc. (mmol/L)
1	2	0.75 ± 0.25	0.75 ± 0.07
2	6	0.87 ± 0.06	2.08 ± 0.10
3	2	1.15 ± 0.25	2.30 ± 0.00
4	3	0.93 ± 0.09	2.43 ± 0.08
5	6	1.13 ± 0.15	2.53 ± 0.13
6	8	0.98 ± 0.03	2.08 ± 0.11
7	6	0.93 ± 0.07	2.17 ± 0.13
Total	33	‘X = 0.97 ± 0.04	‘X = 2.22 ± 0.06

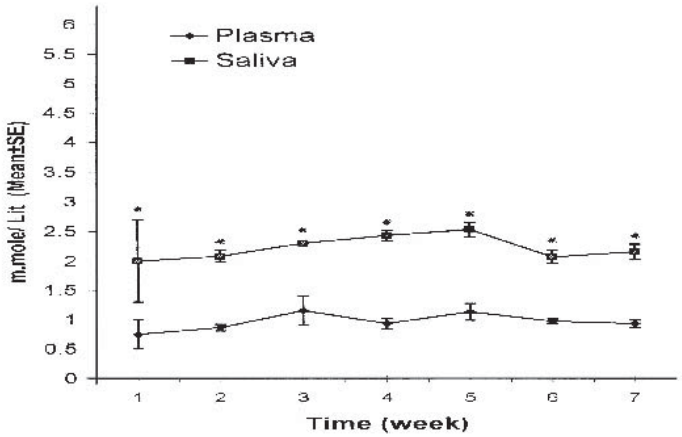

Fig. -1: Comparison between salivary and plasma (serum) Li concentration in Bipolar patients hospitalized at Ahwaz Golestan Hospital, Iran.

lithium concentrations correlation diagram of the 33 patients examined are presented in Fig. 2. The equation for calculating serum lithium from saliva lithium measurements was derived from the graph: Y=0.362 X + 0.166, (Y=serum lithium concentration, X= salivary lithium concentration). The mean lithium concentrations of saliva and serum are presented in Table 7. The mean blood lithium concentration was found to be ('X = 0.97±0.04) and the mean saliva lithium concentration was (X = 2.22±0.06). On the basis of the results obtained in this research and on the basis of statistical calculations, the following equation was obtained: $[Li]_p=0.362[Li]_s+0.166$, where $[Li]_s$=saliva lithium concentration and $[Li]_p$=plasma lithium concentration with correlation coefficient (r=0.58). The 0.166 is a constant which was derived from statistical calculations, 0.362 is the slope of the line diagram of $[Li]_s$ versus $[Li]_p$. On the basis of this equation, and the results obtained in this research, it can be concluded that salivary lithium concentration is always higher than plasma (serum) lithium concentration and the ratio between them is 2.29 and the correlation coefficient is 0.58 (P<0.01). From this equation the required dosage of lithium carbonate for each patient can be determined.[7,8,9] Psychotropic drugs did not affect the concentration of salivary lithium and salivary : serum ratio. The results are similar to those reported by Shopsin.[6] The results obtained in this research demonstrate the possibility of using salivary lithium measurement for monitoring patients on prolonged therapy. Such method may help clinical laboratories to improve the TOM of lithium.

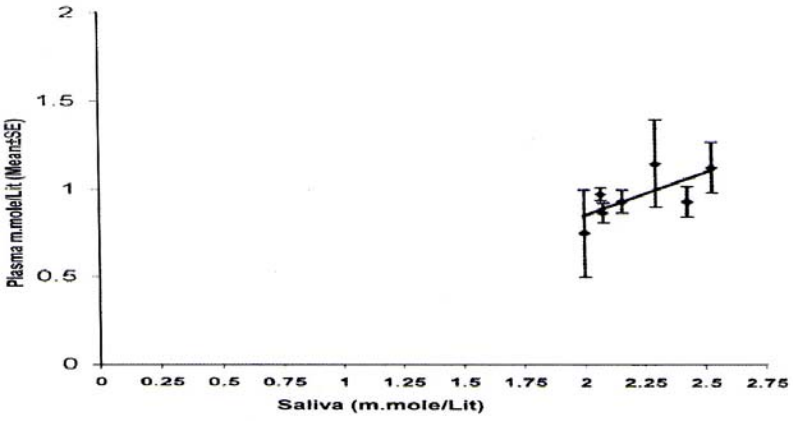

Figure 2. Lithium concentration in plasma (serum) and saliva. The straight line represents the significantly linear correlation between salivary and serum Li concentrations in patients treated with Li_2CO_3 for about three months. The equation for the regression line is $[Li]_p=0.362[Li]_s+0.166$ and the correlation coefficient is r = 0.58 (P<0.01).

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