

Correlation between Serum and Salivary Lithium Levels

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ABSTRACT

The correlation between the serum level and the saliva level of Lithium has been studied in this work. The method used in estimation of lithium levels was flame emission photometry.

These results denote that there is a significant positive correlation between serum and saliva levels. Whether this will be of practical importance or not is a matter for discussion.

However, saliva Lithium estimation may be of importance in assessing the patient's compliance. It may be also of help when there is a difficulty in obtaining blood samples at any time provided that saliva / serum ratio was previously calculated for this particular patient. Noting that the saliva Lithium levels are 200-250% those of serum, the serum level may be, roughly, at times, calculated but with the risk of a probable individual variation.

INTRODUCTION

Lithium has been established as the drug of choice in the treatment of manic-depressive psychosis, manic type, in the prophylaxis of manic episodes and, to a less extent, depressive episodes (Dunner and Fieve, 1978). Other cyclic disturbances as migraine and premenstrual tension may show some improvement under lithium (Schou, 1978).

The therapeutic dose of lithium is close to the toxic dose. Thus, it is extremely important to monitor the patient's serum for lithium regularly, especially at the start of the regimen. This means that the patient should give a sample of blood (5-10 ml) every now and then all through the period of treatment, which is both a tiring and expensive

task (Neu et al., 1975). This has led to the search for another route of investigation to evaluate the course of treatment.

As it was proved that lithium is excreted in saliva in concentrations higher than those in plasma (Good, 1903; Spring and Speirs, 1978) various trials on the clinical application of these findings have been done (Neu et al., 1975; Chick, 1977; Sims et al., 1978). However, some workers have raised many objections to the reliability of saliva lithium in monitoring its level (Sims et al., 1978).

Aim of the work :

The aim of this work is to study the saliva and serum lithium levels in the Egyptian patients; and to compare them with other reported studies; as well as to find out whether the objections raised by previous workers consistently occur.

Method :

Lithium carbonate was given to every patient at about 10 o'clock in the morning daily for 15 consecutive days. Every patient was given two tablets of lithium carbonate and watched closely to ascertain that they were being swallowed. On the 14th day the saliva and serum were collected at about 10 o'clock in the morning. All the patients had breakfast consisting of beans, bread and tea two hours before giving the sample. Saliva was collected examined by flame photometer. Soon after collection of saliva, 5 ml of venous blood were drawn from the antecubital vein. Both serum and saliva samples were taken daily for three successive days following a 14 days course of 800 mg lithium carbonate as a single oral dose per day, i.e. on the 15th, 16th and 17th days.

Results :

Mean daily serum lithium and saliva lithium levels on days 14, 15 and 16 for the whole group of 20 patients :

The mean of serum lithium levels and mean saliva lithium levels for the whole group of 20 patients both males and females were calculated for every day over the three days and the results are given in Table (1).

I. Serum samples :

It can be seen that :

- a) 14th day : The mean serum lithium level was $0.63 \text{ m mol/l} \pm 0.07$ with a range of $0.32 - 1.35 \text{ m mol/l}$ and a coefficient of variation 47%.
- b) 15th day : The mean serum lithium level was $0.61 \text{ m mol/l} \pm 0.05$ with a range of $0.22 - 1.2 \text{ m mol/l}$ and a coefficient of 39%.
- c) 16th day : The mean serum lithium level was $0.61 \text{ m mol/l} \pm 0.05$ with a range of $0.34 - 0.98 \text{ m mol/l}$ and a coefficient of variation of 33.9%.

The significance of the differences in the mean serum lithium levels on the three days was calculated. The differences between the first and second, and second and third and the third and the first days were tested for significance and were ($t = 0.284$, $p > 0.35$; $t = 0.0217$, $p > 0.49$; $t = 0.5102$, $p < 0.3$ respectively). These results suggest the insignificant differences between the mean values for the three days.

II. Saliva samples :

It can be seen that :

- a) 14th day : The mean saliva lithium level was $1.61 \text{ m mol/l} \pm 0.18$ with a range of $0.82 - 2.68 \text{ m mol/l}$ and a coefficient of variation of 40%.
- b) 15th day : The mean saliva lithium level was $1.43 \text{ m mol/l} \pm 0.09$

with a range of 0.80 - 2.24 m mol/l and a coefficient of variation of 28.9%.

- c) 16th day : The mean saliva lithium level was 1.45 m mol/l $\pm$ 0.11 with a range of 0.8 - 2.5 m mol/l and a coefficient of variation of 32.9%.

The significance of differences in the mean saliva lithium levels on the three days was calculated. The differences between the first and second, the second and third and the third and first days were tested for significance and were (t 1.0234, p > 0.15; t 0.1065, p < 0.45; t 1.5001, p > 0.05 respectively). These results suggest insignificant differences between the mean values for the three days.

The mean serum and saliva lithium levels of the three days of the whole sample of patients (both males and females) were calculated (Table 2). It can be seen that :

- The mean serum lithium level was 0.62 m mol/l $\pm$ 0.04 with a range of 0.30 - 1.15 m mol/l and a coefficient of variation of 39.45%.
- The mean saliva lithium level was 1.49 m ol/l $\pm$ 0.11 with a range of 0.81 - 2.47 m ol/l and a coefficient of variation of 32.18%.

The saliva / serum ratio was calculated for every patient according to the mean levels of saliva and serum lithium for the three days (Table 3). The mean saliva / serum ratio was 2.45 with a range of 1.37 - 3.40.

The coefficient of correlation between the mean serum lithium levels and the mean saliva lithium levels was calculated.

For the male group "r" (Coefficient of correlation = 0.8371, "t" for "r" = 4.0478, p < 0.0025, which is very highly significant.

For the female group "r" = 0.73101, "t" for "r" = 3.03005, $p < 0.01$, which is highly significant.

For the whole group of patients (males and females) "r" = 0.7318, "t" for "r" = 4.4209, $p < 0.0005$ which is very highly significant.

TABLE 1

Serum and saliva levels on the 14th, 15th and 16th day after treatment with lithium carbonate in a dose of 800 mg/day for 14 consecutive days in a group of 20 psychiatric patients.

No.	Serum (m mol/l)			Saliva (m mol/l)		
	1st day	2nd day	3rd day	1st day	2nd day	3rd day
1	0.47	0.48	0.52	1.30	1.40	1.40
2	0.63	0.61	0.65	1.40	1.60	1.70
3	0.48	0.73	0.69	1.50	1.40	1.30
4	0.32	0.43	0.40	0.82	1.06	1.00
5	0.36	0.41	0.40	2.55	2.00	2.40
6	0.42	0.56	0.55	0.96	1.10	1.20
7	0.60	0.61	0.60	2.90	1.60	1.65
8	0.60	0.51	0.50	1.40	1.20	1.20
9	0.98	0.91	0.90	2.25	2.00	2.20
10	0.32	0.36	0.34	1.55	0.36	0.90
11	0.90	0.80	0.70	0.36	1.60	1.30
12	0.35	0.40	0.42	0.94	0.90	0.98
13	1.20	0.90	0.98	1.42	1.35	1.40
14	0.57	0.60	0.62	1.30	1.20	1.20
15	0.87	0.82	0.84	2.68	2.24	2.50
16	0.50	0.45	0.52	1.20	1.28	1.20
17	0.34	0.22	0.35	0.82	0.80	0.80
18	0.47	0.40	0.40	1.34	1.24	1.20
19	0.90	0.75	0.92	1.80	1.90	1.80
20	1.35	1.20	0.90	2.40	1.90	1.60
$\bar{x}$	0.63	0.61	0.61	1.61	1.43	1.44
S.E.	± 0.07	± 0.05	± 0.05	± 0.18	± 0.09	± 0.11
S.D.	± 0.30	± 0.24	± 0.21	± 0.64	± 0.41	± 0.48
C.V.	47%	39%	33.9%	40%	28.9%	32.9%

N.B.: The significance of the differences between the mean value of the lithium levels of males and females was calculated and the difference was found to be statistically non-significant ($t = 1.409$; $p > 0.1$). For saliva also the difference was insignificant ($t = 0.396$; $p > 0.35$).

TABLE 2

The mean serum and saliva lithium levels in the whole group of 20 psychiatric patients for the three days.

No.	Serum	Saliva
1	0.49 m mol/l	1.37 m mol/l
2	0.63 "	1.57 "
3	0.62 "	1.40 "
4	0.38 "	0.96 "
5	0.39 "	2.32 "
6	0.51 "	1.09 "
7	0.60 "	2.05 "
8	0.54 "	1.27 "
9	0.93 "	2.15 "
10	0.34 "	1.10 "
11	0.80 "	1.45 "
12	0.39 "	0.94 "
13	1.03 "	1.39 "
14	0.60 "	1.23 "
15	0.85 "	2.47 "
16	0.49 "	1.23 "
17	0.30 "	0.81 "
18	0.42 "	1.26 "
19	0.85 "	1.83 "
20	1.15 "	1.97 "
x	0.62 m mol/l	1.49 m mol/l
S.E.	± 0.04	± 0.11
S.D.	± 0.24	± 0.48
C.V.	39.45%	32.18%

"r" = 0.7318.

"t" for "r" = 4.4269.

p < 0.0005 (very highly significant).

TABLE 3

The saliva / serum lithium ratio according to the mean saliva and serum lithium levels in the three days for the whole group of 20 psychiatric patients.

No.	Saliva/Serum ratio
1	2.79
2	2.49
4	2.51
5*	6.03
6	2.14
7	3.40
8	2.36
9	2.31
10	3.29
11	1.93
12	2.42
13	1.34
14	2.07
15	2.93
16	2.52
17	2.78
18	2.98
19	2.16
20	1.71
x	2.45

(*) In the statistical analysis of the mean of the saliva / serum ratio, the ratio, the values obtained from the patient number 5 were excluded due to their oddness, being extremely high.

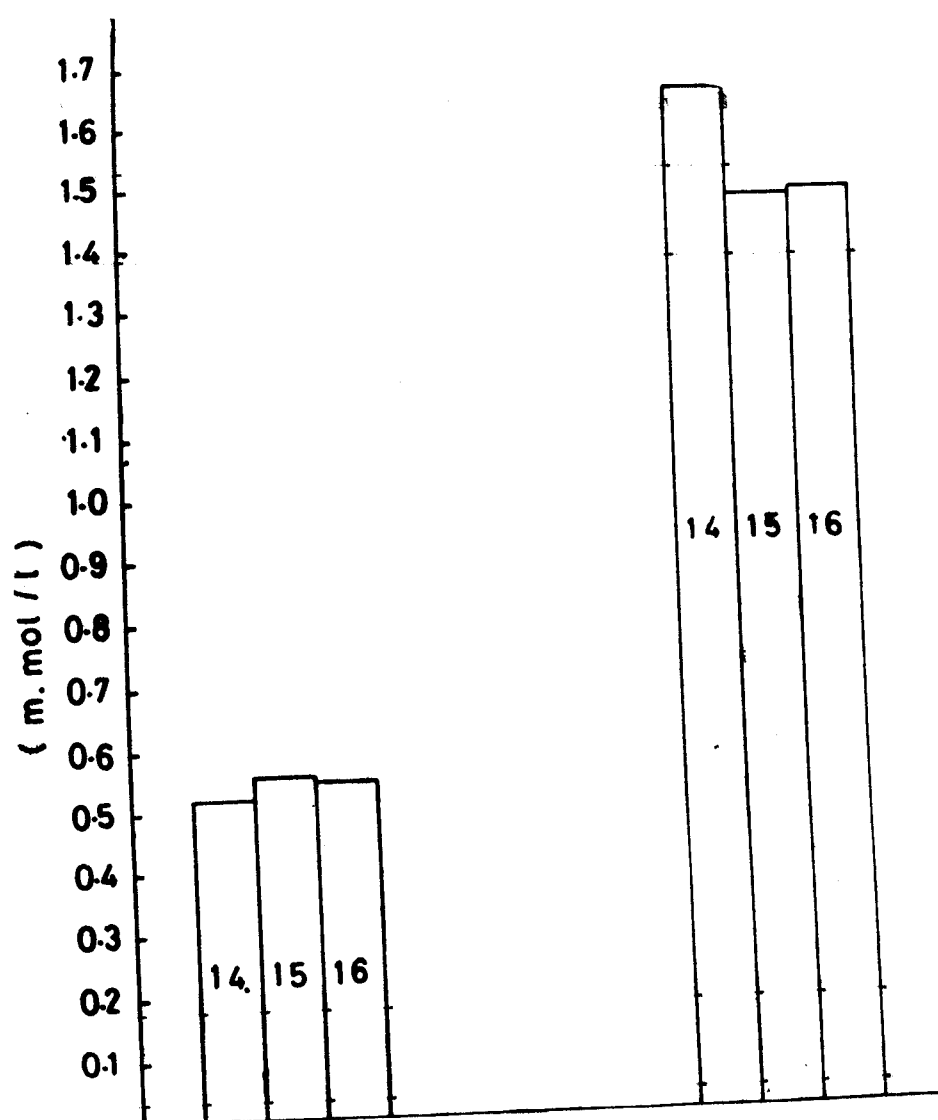


Fig. (1) Bar-Chart Showing the Mean Serum and Saliva Lithium of the Male Patients on the 14th, 15th and 16th days.

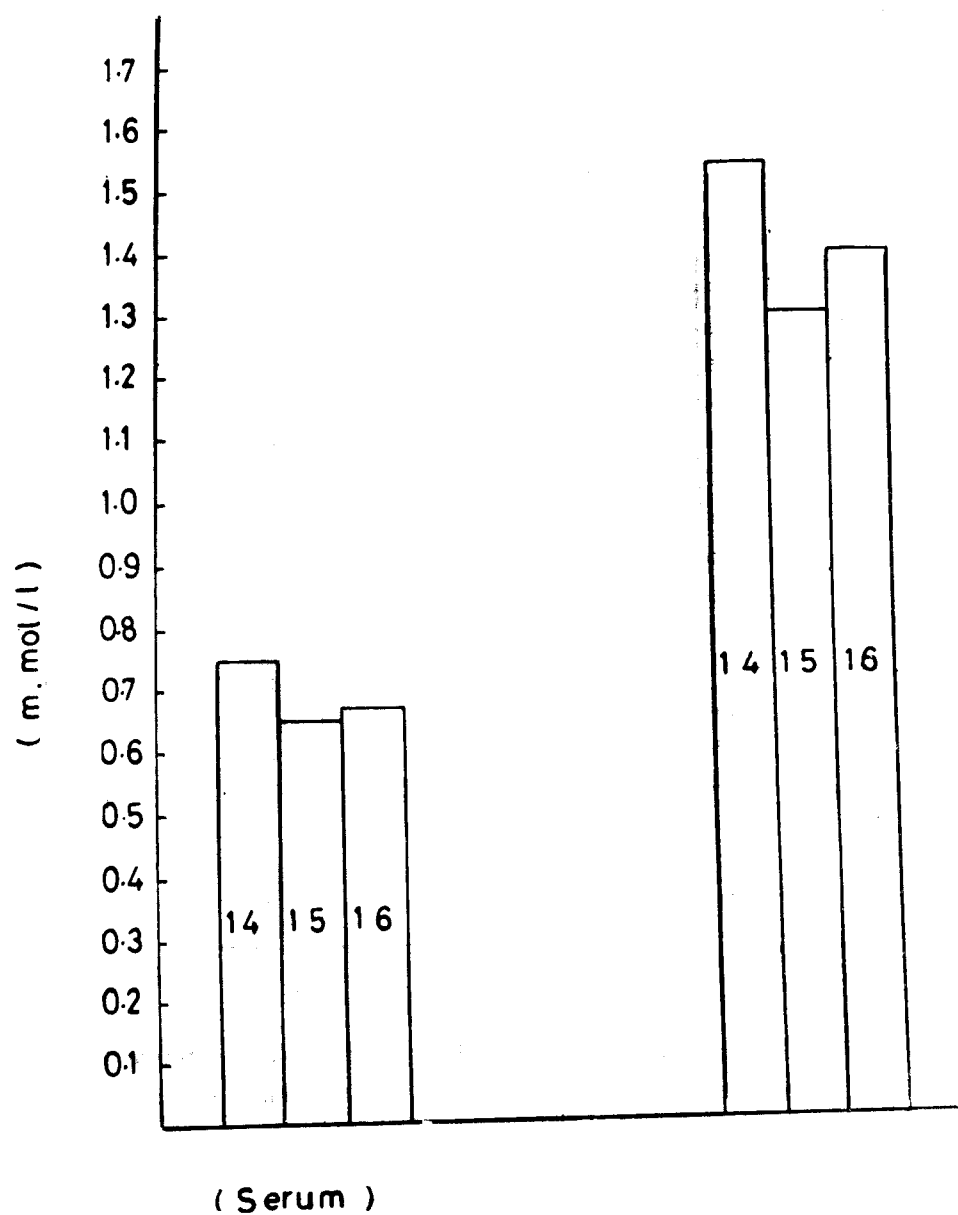


Fig. (2) Bar-Chart Showing the Means of Serum and Saliva Lithium Levels in the Female Patients on the 14th, 15th and 16th. days.

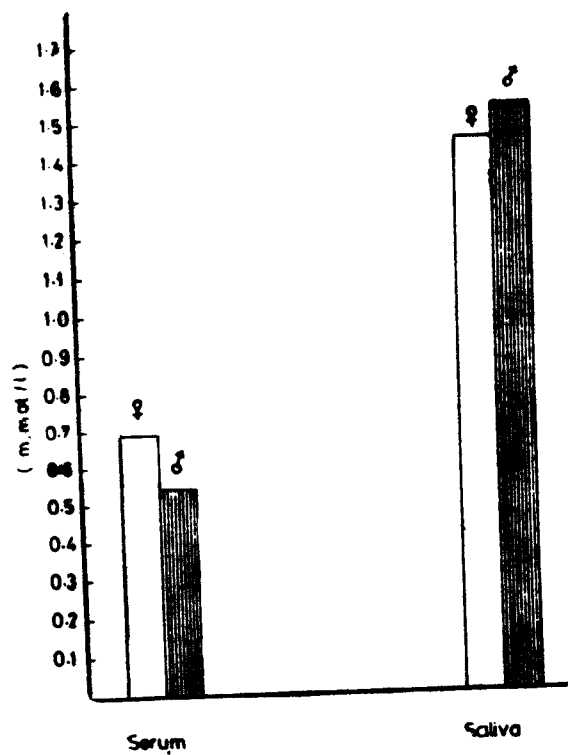


Fig. (3) Bar-Chart Showing the Mean of the 3 days of Serum Lithium and Saliva Lithium for Male and Female Patients.

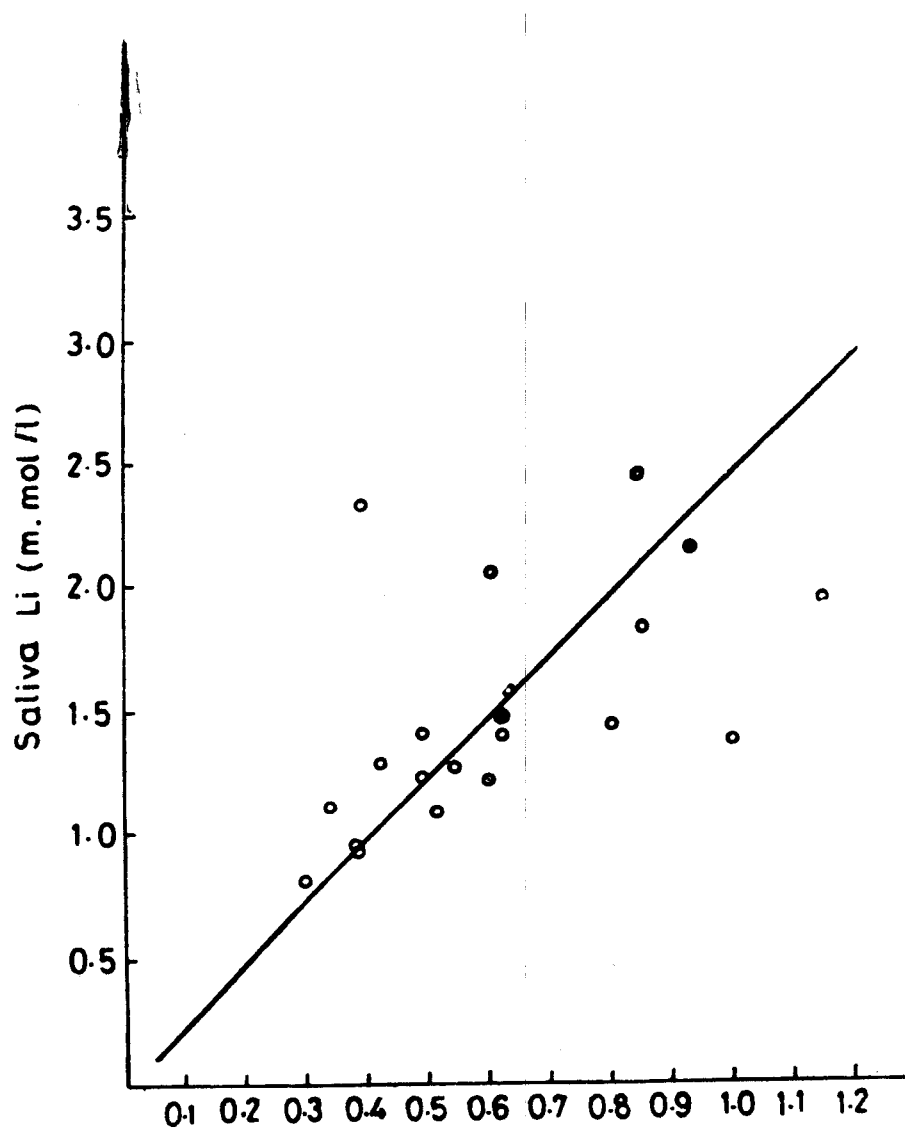


Fig. (4) Relation Between Lithium Levels in Serum and Saliva for the Group of Patients Studied.

Discussion :

The rationale for monitoring drug levels is that, for many drugs, there is a close relationship between their biological effects, both therapeutic and toxic, and the serum concentrations. The relationship, however, depends upon several factors such as the mechanism of action, the pharmacokinetics of the drug and the responses of the target systems in the patient.

The ability to accurately determine levels of lithium in a patient's serum has contributed enormously to the safety and efficacy of its use. In fact, serious toxic reactions can develop as a result of poor monitoring (Agulnic *et al.*, 1972). It is recommended that serum levels be obtained frequently (as often as every 48 hours during the first week) at the outset of lithium therapy, in order to titrate the drug administration to therapeutic levels which are in the range of 0.6 m mol/l to 1.2 m mol/l, and to avoid exceeding 1.5 m mol/l which is near to toxic level (Neu *et al.*, 1975).

In recent years assay of saliva has been explored as another source of monitoring drug concentrations (Speirs *et al.*, 1971; Groth *et al.*, 1974). Saliva has obvious advantages but also a number of disadvantages.

Among the advantages offered by monitoring of salivary drug level is that repeated samples of saliva can be collected without much discomfort to the patient. Serum and saliva samples were taken synchronously in search of a correlation between the saliva lithium and serum lithium levels. Moreover, sampling was done on three consecutive days in order to calculate a mean saliva / serum ratio for each individual as recommended by Chick (1977). Mixed saliva and not salivary secretion from individual glands was used in this study. The collection of mixed saliva is simply done by asking the patient to spit into a container.

The mean serum lithium level obtained in the present work for the

group of 20 patients was 0.62 m mol/l and that for saliva 1.49 m mol/l. These findings are near to those obtained by Neu *et al.*, (1975) who reported a mean of 0.69 m mol/l for serum and 1.56 m mol/l for saliva lithium. Moreover, from a scatter diagram presented by Verghese *et al.*, (1977) serum and saliva lithium levels reached a level of 0.7 m mol/l and 1.7 m mol/l respectively. On comparing and analysing statistically the results obtained for the male group of patients with those of the female group no significant differences were found i.e. the serum and saliva levels were not affected by the sex of the patient. This provides further support to the rationale of considering the sample of patients as one homogeneous group as has been achieved by many workers (Neu *et al.*, 1975 and Sims *et al.*, 1978 and Verghese *et al.*, 1977) respectively.

The findings obtained in this study show that there is a positive correlation between the salivary and serum lithium levels. This correlation, although not very high, is statistically highly significant. The values obtained in this study are very near to those obtained by other workers in different geographical regions (Neu *et al.* "U.S.A."; Verghese *et al.* "India"; Sims *et al.* "Great Britain"); denoting that the correlation is neither the function of climate nor race. The ratio of saliva/serum lithium level is about 200 - 250% the serum level.

The coefficient of correlation between serum and saliva lithium levels for the whole sample of patients was 0.7318 ($p < 0.0005$), i.e. a positive correlation does exist between the serum and saliva lithium levels. For the male group the coefficient of correlation was 0.8371 ($p < 0.0025$), which is higher and more significant than that for the female group 0.73101 ($p < 0.01$).

These results indicate that :

A positive correlation coefficient is 0.7318 for the whole group of patients, slightly less for the females and slightly higher for the males.

This correlation is very highly significant ($p < 0.0005$).

Neu *et al.*, (1975) have obtained a correlation coefficient of +0.9; Verghese *et al.*, (1977) gave a figure of +0.88 ($p < 0.01$), while Sims *et al.*, (1978) gave a figure of +0.1 ($p < 0.001$). The coefficient of correlation obtained in this work is nearer to that obtained by Sims *et al.*, (1978), which points to a lower correlation than that referred by the other two studies.

The saliva/serum lithium ratio was in the range of 1.34 - 3.40, with a mean of 2.45 which is near to a mean ratio of 2.26 and to 2.16 which were reported by Neu *et al.*

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ABSTRACT

**Une corrélation entre les niveaux de lithium dans
le sérum et dans la salive.**

La corrélation entre les niveaux de lithium dans le sérum et dans la salive a été étudiée dans cette recherche. La méthode employée pour estimer les niveaux de lithium fut l'émission de flamme mesurée par le photomètre.

Les résultats ont montré qu'il y avait une corrélation significative entre les niveaux de lithium dans le sérum et dans la salive. Soit que cela aurait une importance pratique ou non est encore un problème discutable.

Cependant l'estimation du lithium dans la salive peut être un moyen de mesurer la compliance du patient. Aussi, cette manœuvre peut-être appliquée dans les cas où il est difficile d'obtenir des échantillons de sang, à n'importe quel moment, à condition que le rapport salive / sérum soit antérieurement connu chez ce patient, en particulier. A noter que les niveaux de lithium dans la salive sont de 200% - 250% ceux du sérum, le niveau du lithium dans le sérum peut-être calculé approximativement tout en considérant le risque probable de l'existence d'une variation individuelle.

الارتباط بين مستوى الليثيوم في البلازما وفي اللعاب

جري دراسة الارتباط بين مستوى الليثيوم في البلازما وفي اللعاب واستعمل في قياس مستوى الليثيوم طريقة قذف اللهب الفلوميترى .

وقد أظهرت النتائج أن هناك ارتباط إيجابي بين مستوى الليثيوم في البلازما ومستوى اللعاب ، أما مدى الأهمية العملية لهذا الارتباط فإن ذلك مجال نقاش لم يحسم .

وعلى أى حال ، فإن فحص الليثيوم في اللعاب ، قد يبدو هاما في تقييم التقدم في حالة المريض ، كما قد تكون عاملا مساعدا حين توجد صعوبة في أخذ عينة دم في أى وقت باعتبار أن نسبة اللعاب / البلازما قد سبق حسابها في هذا المريض بالذات ، وإذا لاحظنا أن مستوى الليثيوم في اللعاب يبلغ ٢٠٠ الى ٢٥٠٪ بالنسبة لمستوى الليثيوم في البلازما فإن المستوى في البلازما يمكن أن يحسب تقريبا في بعض الأحيان ولكن مع مخاطرة احتمال وجود اختلافات فردية .