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RELIABILITY OF SALIVA LITHIUM LEVEL—A PROSPECTIVE STUDY

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SUMMARY

140 synchronous samples of serum and saliva, collected from 28 patients undergoing lithium therapy, were studied. The mean saliva/serum lithium ratio calculated for the first 120 synchronous samples from 24 patients was found to be 2.68 (population mean ratio). Regression line equation calculated for the same population came out to be $Y=0.325 + 0.22X$. Predictive value of saliva lithium level was tested by applying this regression equation and the population mean ratio on 20 samples from the next 4 patients. Prediction was also tried in the 24 patients who had given more than 3 synchronous samples by using the individual mean saliva/serum lithium ratio. An individual's mean ratio was calculated from the initial 3 synchronous samples and the predictive value of saliva was tested on subsequent samples in the same patient by using his mean ratio. This method of prediction was found to be better than predicting on the basis of population figures. But no method was found to be consistently reliable and therefore saliva lithium level is not a reliable indicator of serum lithium concentration.

In recent years, saliva has been tipped as a possible substitute of serum for estimation of lithium concentration in the body (Shopsin *et al.*, 1969 ; Spring and Spirtes, 1969 ; Lazaras *et al.*, 1973 ; Groth *et al.*, 1974 ; Neu *et al.*, 1975 ; Verghese *et al.*, 1977). However there have been differing opinions regarding the reliability of saliva lithium levels. On reviewing the literature on this subject, there appear three major trends of thought regarding the relationship between serum and saliva lithium levels : (i) There is a constant ratio between saliva and serum lithium level (Shopsin *et al.*, 1969 and Lazaras *et al.*, 1973). These authors propose that saliva can be used to estimate the serum lithium concentration. (ii) Saliva/serum lithium ratio varies between individuals (Groth *et al.*, 1974 ; Neu *et al.*, 1975 and Ravenscroft *et al.*, 1978). These authors advocate that a mean saliva/serum lithium ratio should be calculated for each individual, which can be used to predict serum lithium level in that particular individual. (iii) Because of both inter-individual and intra-individual variations in ratio, saliva lithium levels are not reliable (Sims *et al.*, 1978 ; Mathew *et al.*, 1979 and Vlaar *et al.*, 1979).

Shopsin *et al.* (1969) proposed the usefulness of regression line equation method for predicting the serum lithium concentration. According to them, the serum lithium level in a patient could be estimated from his saliva lithium level, by using the regression line equation obtained for a population. Verghese *et al.*, (1977), in a small-sample study, suggested that the mean saliva/serum lithium ratio calculated on a population of patients such as their's, would help in predicting the serum lithium concentration by saliva estimations. According to them, the therapeutic range of saliva lithium would be 1.5-3.0 m eq/L. Our present endeavour aims at evaluating the usefulness of saliva lithium estimation in predicting the serum lithium level for clinical purposes, by a predesigned, prospective study.

MATERIAL AND METHODS

Twenty eight patients (24 M, 4 F) .

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belonging to the age group of 15 to 59 years, attending the 'Lithium Clinic' of the Department of Psychiatry, Institute of Medical Sciences, at the Banaras Hindu University, Varanasi, during the period August 1979—May 1980 comprised the clinical material. Of 28, 14 patients were in the manic phase, 7 in depression, 5 in remission and 2 were diagnosed as schizo-affective at the time of study. The patients were admitted in the ward for the study period. The average duration of stay in hospital for each patient was 24 days.

Samples of serum were collected by drawing 5 ml of venous blood in a sterile centrifuge tube and allowed to clot at room temperature. All samples were drawn between 8 and 8.30 a.m. before that day's morning dose, ensuring a gap of 12 hours after the previous night's dose. Within five minutes of collecting the blood, samples of saliva were collected. Patients were given a rubber piece for chewing and were instructed to collect 5 ml of saliva in a sterile test tube after discarding initial 2 minutes' secretion. Serum was separated by centrifuging. Similarly saliva samples were also centrifuged to separate mucus and other particles. Lithium was estimated with digital flame emission photometry by the method recommended by Amdisen (1967). Estimations were done on the same day of collecting the samples. Only samples collected after 2 weeks of starting lithium were included for the study. Samples were collected at intervals of 2 days (3) and then once a week. Number of synchronous samples for each patient varied from 3 to 8 (A pair of serum and saliva samples collected from a patient at the same time was considered as one synchronous sample).

Method of Analysis : Routine statistical methods were employed to find the mean and standard deviation. Values of saliva and serum lithium were subjected to correlation coefficient analysis. Regression equation was calculated by least squares method for predicting the serum lithium levels from observed saliva lithium levels.

The observations were analysed in two phases. In the first phase, values of the first 120 synchronous samples collected from 24 patients were grouped together. Mean saliva/serum lithium ratio (population mean ratio) and regression line equation for this population were calculated. The population mean ratio and regression equation thus obtained were applied on the remaining 20 samples of 4 patients to test how far, with the help of these population figures, we can predict serum lithium levels from the available saliva values. We then compared the predicted serum lithium levels with the corresponding observed (real) serum levels.

In the second phase, 24 patients who had given more than 3 synchronous samples were selected. Mean saliva/serum lithium ratio was calculated for each of these 24 patients using the initial 3 synchronous samples (Individual mean ratio) as suggested by Chick *et al.* (1977). With the help of individual mean ratio, serum lithium levels were predicted in these patients on subsequent occasions using observed saliva lithium levels. We had a total of 56 synchronous samples in which prediction could be done by this method. The predicted serum lithium levels were then compared with the corresponding observed (real) serum concentrations to test the accuracy of prediction.

For the purpose of this study, a difference within the range of ± 0.2 meq/L between predicted and observed serum levels was arbitrarily taken as acceptable, a wider difference making the prediction unsatisfactory.

RESULTS

The present study revealed a statistically significant correlation between saliva and serum lithium levels ($r=0.71$, $p<0.001$ for $N=140$). The mean saliva/serum lithium ratio (population mean) calculated

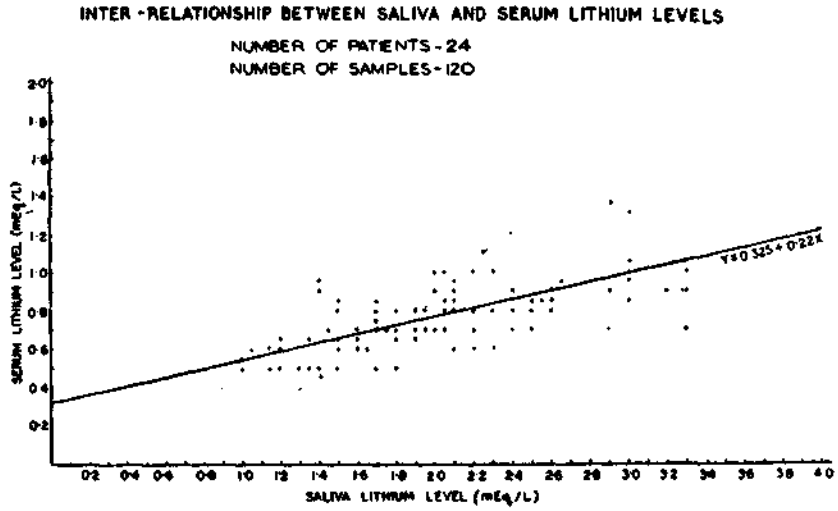

Fig. 1

for first 120 samples was found to be 2.68. Incidentally this is higher than the ratios found by Neu *et al.* (1978) and Verghese *et al.* (1977) who reported respective ratios of 2.26 and 2.22 from their small-sample studies. The regression line equation obtained for the population came to be $Y=0.325+0.22X$, wherein Y=predicted serum lithium level and X observed saliva lithium level (Fig. 1).

Serum lithium levels predicted on the basis of regression equation differed considerably from the corresponding observed (real) serum concentrations. We observed that when the real serum lithium concentration was in the lower therepeutic range, the saliva/serum lithium ratio appeared to be more constant, which in turn gave

TABLE : *Prediction of serum lithium level by saliva estimations : Comparison of three methods.*

Method	Samples tested	Prediction satisfactory	Percentage
1. Regression line equation method Y=0.325 +0.22X(n= 120)	20	9	45.0
2. Population mean ratio method mean ratio : 2.68(n= 120)	20	14	70.00
3. Individual mean ratio method	56	45	80.40

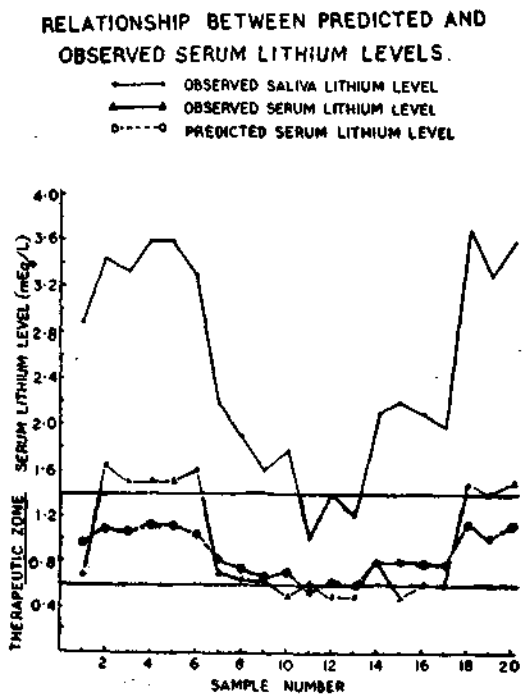

Fig. 2

better predicted serum values. When the real serum lithium level was in the higher therapeutic range and at grossly sub-therapeutic level, the prediction tended to vary considerably from observed serum values (Fig. 2). When serum lithium levels were predicted on the basis of population mean ratio, the predicted serum levels were more often satisfactorily close to the real values (70%) whereas with regression equation method, the prediction was less often (45%) satisfactory. However, as shown in the Table, when individual mean ratio was utilised instead of the population figures predictions were most often satisfactory (80.4%). Inability to have a universally applicable formula is obviously due to inter-individual variation in saliva/serum lithium ratio. In our study, the individual ratios varied between 1.8-3.8. Even intra-individual variation in the saliva/serum lithium ratio seems to be significant and cannot be ignored. In our study, in one patient, the ratio varied from 1.6-4.4 and in another, between 2.4-4.7.

DISCUSSION

We have tried to evaluate saliva lithium as a predictor of serum lithium concentration by two major approaches, i.e. by population method (Mean ratio as well as regression equation) and by individual mean ratio.

Despite a positive correlation between saliva and serum lithium levels ($r=0.71$ $p<0.001$), our attempt to predict the serum lithium level by saliva lithium estimation did not succeed that often. Our sample size was reasonable and we adopted a uniform standard for collection of samples (which were synchronous), yet predicted values often differed markedly from the real values. We, further adopted a liberal criterion for satisfactory prediction and even then, the individual mean ratio approach which is best among the 3 methods tested (after 3 synchronous samples) left behind 20% unsatisfactory prediction. Shopsin *et al.* (1969), found a consistent concentration gradient between saliva and serum lithium levels. On the basis of a regression equation calculated on a small heterogenous sample, they proposed to predict serum lithium concentration from saliva. In this study, we have obtained a regression equation based on a sufficiently large number of synchronous samples ($n=120$). But efforts to predict serum lithium level from saliva on the basis of the equation, did not give satisfactory results. Only in 9 samples out of 20 (45%) the predicted serum lithium levels were within ± 2 meq/L of observed serum levels. By using the population mean ratio obtained for 120 synchronous samples (2.68), we could not reliably predict serum lithium levels from saliva values. However, the prediction is more satisfactory i.e. in 14 out of 20 (70%) when compared to the regression equation method (45%). Our observations in the present study indicate that, though population mean ratio method is more reliable than the regression equation method, both these methods do not appear to be useful in a clinical setting. The reasons for this may be multiple, which are obscure at the moment, but individual differences in lithium distribution in the body in various body fluids may be one of the possible factors. Revenscroft *et al.* (1978), observed that inter individual variation in saliva/serum lithium ratio was much more than intra-individual variation. They proposed to use individual mean ratio for predicting the serum lithium level from saliva, for that individual. Similar conclusion had been drawn by Groth *et al.* (1974) and Neu *et al.* (1975). Our attempt to predict serum lithium level from saliva by way of individual mean ratio has shown a relatively reliable prediction compared to the two previous methods which depend upon the population figures. We observed that individual patients tended to have a consistent ratio but there were sudden and sporadic fluctuations, which are difficult

to explain.

It can be concluded that predicting the serum lithium level from saliva estimations with the help of regression equation is not a reliable procedure. The population mean saliva/serum lithium ratio is relatively better and the individual mean saliva/serum lithium ratio is still better. But even with the best of the methods predictions will be grossly inaccurate (more than ± 0.2 meq/L in about 20% of the samples).

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