SERUM LITHIUM LEVELS WITH SLOW-RELEASE AND CONVENTIONAL LITHIUM CARBONATE PREPARATION

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SUMMARY

Eighteen physically healthy volunteers were given 1200 mg of standard and sustained-release preparations of lithium on two different occasions. Serum lithium levels were estimated at four-hourly intervals and statistically analysed. The findings and the results have been discussed with particular reference to their implications for future research.

Lithium is an effective drug in the prophylaxis of manic depressive psychosis (Hullin et al., 1972). For its prophylactic effect, it should be taken regularly and serum lithium should remain within therapeutic range (Fieve, 1976). The conventional lithium carbonate preparations are usually given in three or four divided doses daily (Cooper et al., 1978). However, it is clearly established that a patient is more likely to forget to take a dose in several times a day regimen than in once a day regimen (Ayd, 1974) ; hence a sustained release preparation which is taken once a day may have distinct advantage over the conventional preparations. The studies conducted in various countries with such preparations have shown that they are not sustained release preparations but only slow release preparations (Coppen et al., 1969 ; Persson, 1974 ; Crammer et al., 1974 ; Fryro et al., 1970 ; Amdisen, 1975 ; Tyrer et al., 1976 & Marini & Sheard, 1976). It has been reported on the one hand that at least three such slow release preparations (Camcolit, Norgine, Limited, Britain ; Priadel, Delandale Laboratories, Britain ; Phasel, Pharmax Limited, Britain) show slow release only in vitro and not in vivo ; there is no difference between the rate of absorption and excretion of these three slow release preparations and conventional preparations, and at least one of these preparations (Phasal) is very poorly absorbed (Tyrer et al., 1976). On the other hand, another slow-release preparation (Rowell Laboratories, Inc., Bandette, Minn., U.S.A.) has been reported to produce less post dose lithium level variability as compared to a standard release preparation (Cooper et al., 1978). Similarly lower and less steep serum lithium peaks have been reported with a plastic matrix type of slow release preparation than those occurring with conventional tablets (Amdisen, 1969). Such seemingly conflicting reports from foreign studies and the fact that no study with slow release lithium preparation has been conducted in India, motivated us to undertake this study.
AIM

To compare the serum lithium levels produced by single dose of standard release lithium carbonate preparation (Licab, Torrent Laboratory, Ahmedabad, India) & slow release lithium carbonate preparation (Priadel, Delandale Laboratories, U. K.)

MATERIALS AND METHOD

The sample of the present study consisted of eighteen volunteers who were physically normal on a detailed clinical examination. Their base-line haematological investigations (Haemoglobin%, total & differential leukocyte counts & general blood picture) urine examination, blood urea, serum creatinine & serum electrolytes also were within normal limits. Throughout the period of the study (8 days) they were kept in the hospital on a standard hospital diet containing not less than 6 gm/day of sodium chloride and adequate water intake was ensured. The timings of distribution of breakfast, lunch & dinner were the same for each so as to neutralize any interference with absorption of the lithium tablets due to presence of food in gastro-intestinal tract which is known to produce wide changes in serum lithium levels (Amdisen, 1969). In the first phase of the study, all the volunteers were given 1200 mg of slow release lithium carbonate preparation in a single dose with 500 cc of water, one hour after the morning meal. The blood samples were drawn at four hourly intervals for the next twenty-four hours. All the volunteers were closely watched for development of any sign of lithium toxicity.

In the second phase of the study, conducted six days after the first phase of study, the same volunteers with similar timings, schedule and precautions were given 1200 mg of standard release (conventional) lithium carbonate preparation in single dose and blood samples were drawn in a similar manner.

The serum lithium level was estimated by flame photometry which is an easy, rapid and sensitive method (Amdisen, 1967) and the results were compared.

Observations:

No signs of lithium toxicity were observed in any of the volunteers.

The data collected revealed that—

(1) If 0.6 to 1.5 mEq/l, is taken as range of therapeutic serum lithium level, the number of toxic, therapeutic and sub-therapeutic serum lithium values in relation to slow-release and conventional lithium preparations were 23 (21.3%) & 63 (58.3%); 22 (20.4%) & 0 (0%); 102 (94.4%) & 6 (5.6%) respectively. The time of peak value ranged from 4 to 24 hrs.

(2) 7 volunteers had a serum lithium level of 0 mEq/l after 12 hours of intake of long acting lithium. None of the volunteers revealed serum lithium level of 0 mEq/l while taking short acting lithium.

Table 1 shows the comparative statistical analysis of the serum lithium values with slow release and conventional lithium preparations. The mean serum lithium levels were consistently higher after intake of slow release lithium preparation than after intake of conventional lithium preparation except after twelve hours of intake when this relationship was reversed. Standard deviations were consistently higher for slow-release lithium preparation. There was a statistically significantly difference in corresponding serum lithium levels obtained with slow-release & conventional lithium after 4 hrs. (p<.01) 12 hrs. (p<.001) 20 hrs. (p<.001) & 24 hrs. (p<.05) after intake. There was no statistically significant correlation in corresponding serum lithium values obtained with slow release & conventional lithium preparations. The co-
TABLE 1—Comparative Statistical Analysis of the Serum Lithium Values

| Sets of Comparison                                      | Mean        | Standard Deviation | Values of 't' | Values of correlation coefficient (r) |
|--------------------------------------------------------|-------------|--------------------|---------------|--------------------------------------|
| Serum lithium values with long & short acting lithium after four hours | 1.283 & 0.894 | 0.508 & 0.346      | 3.07**        | 0.296                                |
| Serum lithium values with long & short acting lithium after 8 hours | 1.056 & 1.017 | 0.464 & 0.343      | 0.49          | 0.233                                |
| Serum lithium values with long & short acting lithium after 12 hours | 0.239 & 0.867 | 0.283 & 0.274      | 6.42***       | 0.429                                |
| Serum lithium values with long and short acting lithium after 16 hours | 0.972 & 0.889 | 0.375 & 0.197      | 1.16          | 0.059                                |
| Serum lithium values with long & short acting lithium after 20 hours | 1.339 & 0.956 | 0.469 & 0.206      | 3.88***       | 0.450                                |
| Serum lithium values with long & short acting lithium after 24 hours | 1.017 & 0.890 | 0.338 & 0.171      | 2.60*         | 0.268                                |

*p<.05   **p<.01   ***p<.001

TABLE 2—Comparison of Mean Serum Lithium Level Variations

| Sets of Comparison                                      | Long acting Lithium | Short Acting Lithium | Value of 't'   |
|--------------------------------------------------------|---------------------|----------------------|----------------|
| Difference between serum lithium values after 4 and 8 hours | 0.239               | —0.1222              | 2.156*         |
| Difference between serum lithium values after 4 and 12 hours | 1.04                | 0.00                 | 8.487***       |
| Difference between serum lithium values after 4 and 16 hours | 0.3400              | 0.06111              | 2.97**         |
| Difference between serum lithium values after 4 and 20 hours | —0.055              | —0.06                | 0.060          |
| Difference between serum lithium values after 4 and 24 hours | —0.2556             | 0.3297               | 1.065          |

*p<.05, **p<.01, ***p<.001

The coefficient of skewness (not shown in Table 1) was computed to find out the normality of distribution of serum lithium values and it was found to be positively skewed in relation to both the preparations. The coefficient of kurtosis (not shown in Table 1) revealed that the magnitude of serum lithium values in the positively skewed distribution curve did not follow any consistent pattern in relation to any of the two preparations.

Table 2 shows the comparisons of mean serum lithium level variations for long and short acting lithium preparations as calculated from the mean difference between 4 hour serum lithium level (taken as baseline lithium level) and the subsequent serum lithium levels. Such differences were significantly more on the higher side with long acting lithium in 4 vs. 8 hrs (p<.05), 4 vs. 12 hrs. (p<.001) & 4 vs. 16 hrs. (p<.01) sets of values.
RESULTS AND DISCUSSION

Absence of any side effects contradicts the reports of some previous studies (Persson, 1974; Persson, 1971; Fyro et al., 1970) where diarrhoea was commonly reported only with slow-release preparations.

Majority of the serum lithium values (94.4%) with single dose of short acting lithium preparation were within therapeutic range whereas only 58.3% of serum lithium values with long acting lithium preparations were within therapeutic ranges. This finding very highly suggests that it is possible to administer short acting lithium preparation only once a day for therapeutic purposes. The chances of toxic serum lithium levels are 0% & those of subtherapeutic levels are minimal (5.6%). It appears that conventional lithium preparation is superior to slow acting lithium (when both are given as once a day schedule) in maintaining therapeutic blood levels and is also less likely to produce very high or very low levels. This finding sharply contrasts with that of another study (Tyrer et al., 1976) where a single dose of the same slow release preparation (Priadel) produced therapeutic levels in all the eight subjects at the height of peak; mostly sub therapeutic levels after 12 and 24 hours and toxic levels in none. It is difficult to explain such a vast difference completely but the following factors may be partly responsible for it—

(A) Lesser dose of drug given (1000 mg in Tyrer et al.’s study compared to 1200 mg in present study).

(B) Relationship of lithium intake to time of food intake (fasting stomach in Tyrer et al.’s study compared to after breakfast in present study). It is known that conventional lithium preparations given with meals can produce almost double serum lithium levels of those obtained in early mornings without meals (Amdisen, 1969).

Absence of lithium in serum in 7 volunteers after 12 hours shows that there may be some factor (disintegration of tablet, erratic absorption etc.) which operates only with long acting preparation whereby sometimes isolated, unpredictable and abnormally low serum lithium values may be obtained. As in this study, with single dose of Priadel, Coppen et al. (1969) also found widely varying times of peak values ranging from 3 to 24 hours.

The standard deviations of serum lithium values with slow release preparation were consistently higher than those with conventional lithium preparation, suggesting that the variations in serum lithium levels are more with slow release preparation than with the conventional one. With the same preparation (Priadel) Coppen et al. (1969) have reported similar findings. Amdisen (1969) found lesser variability and lower serum values with slow-release lithium preparation than with conventional lithium preparation but his findings cannot be compared with those of this study because he had given both slow & standard release preparations in three divided doses in a day & had used another type of slow-release preparation (Plastic Matrix type). The mean serum lithium levels were usually (3 out of 4 significant values) significantly higher with slow-release lithium preparation than with conventional preparation. It suggests that relatively lower doses of slow release lithium than conventional lithium may be required for therapeutic purposes (however, it will also greatly enhance the chances of sub therapeutic levels which were found in as high as in 20.4% of total observations in this study. Cooper et al. (1978) also found that slow release and conventional lithium preparations given in single dose were not bioequivalent.

There was no significant correlation between the corresponding serum lithium values with slow and standard release preparations suggesting that those who have
"experience" with the use of conventional lithium preparations cannot readily apply their experience to slow-release preparations.

Since the coefficient of kurtosis did not follow any consistent pattern in case of either of the two preparations and the mean serum lithium level variations were consistently higher in all the five sets of values with slow-release preparation (and significantly so in three sets of values), it can be inferred that unpredictable high serum lithium level will be much likely to occur with slow-release preparation than with conventional lithium preparation.

In view of the findings of the present study, it will be desirable to be cautious in using slow release forms of lithium until such times that further studies undertaken on larger samples prove its advantage over conventional preparations.

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