

A BI-COMPARTMENTAL MODEL SYSTEM FOR LITHIUM KINETICS IN MANIA

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SUMMARY

Lithium $T_{1/2}$ has been determined from L_p decay. It is clear that calculation of a single $T_{1/2}$ from L_p decay is essentially incorrect as the decay is not exponential. The same data points have been analysed on a kinetic model yielding 3 different half lives too. The implication of the study is that the plasma and the erythrocyte systems undergo many local steady states instead of any global steady state. The rate of movement of Li^+ across plasma and erythrocyte undergoes fluctuations and may exhibit many more different half lives over a time period in either direction.

Lithium is the drug of choice in the treatment of affective disorders. It is used in the treatment of acute mania and for prophylaxis in MDP (circular) and recurrent unipolar depressions. A serum level more than 2 mmol/L is considered to be toxic (Stromgren and Schou, 1964). The clinical dosage regimen is usually fixed by serum lithium estimations. However, Schou et al. (1954) have emphasized that clinical observation should form the main basis of dosage adjustment and control of the treatment.

Amdisen (1967) suggested that the blood samples for lithium estimation can be taken atleast 10-15 hours after the intake of the last lithium dose and should be fixed below a level of 1.6 mmol/L. Since the difference between the toxic and effective doses of lithium is relatively small, the dosage schedule for lithium is critical both in terms of time and concentration regimens.

Currently $T_{1/2}$ of lithium has been determined by regression analysis of plasma lithium decay for a very large population.

(Amdisen, 1975, and Lyttkens et al. (1976). High intracellular lithium concentrations have been found to be associated with toxic manifestations and E.E.G. abnormalities (Zakowska Dabrowska and Rybakowski, 1973). Also a high L_c/L_p ratio has been found to be of significance in responders to non responders, but controversy as regards the utility of interacellular lithium estimation still remains.

The present study critically evaluates the lithium kinetics on a bi-compartmental model system, to determine the significance of such estimations during therapy.

Materials and Methods :

Only bipolar MDP (currently manic) cases ($n=16$) were selected for the present study who satisfied Feighner's (1972) diagnostic criteria for mania. The diagnosis was confirmed by 2 independent psychiatrists. They were on regular hospital diet without any other extra diets from outside. They were not on any other medication prior to hospitalization. The age range

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was 20-40 years. They were considered to be good candidates for lithium prophylaxis according to the criteria of Schou & Thomson (1975). They were given 1,200 mg of Lithium Carbonate in 3 divided doses daily and the blood samples collected for estimation of plasma lithium (Lp) and erythrocyte lithium (Le) concentrations every third day within 10-12 hours of the last dose. After a period of two weeks the drug was discontinued but blood samples collected for Lp and Le estimations for 18th and 20th days. The serum estimations were done by procedure described (Coombs, 1971) and the erythrocyte lithium estimation was done by a procedure developed and standardized in the Institute by Pradhan (1978). Rating scale of Patterson *et al.* (1973) was employed to evaluate the clinical state during this period by two independent psychiatrists.

Theoretical Considerations :

In two compartment system, $\vec{C}_1 \rightleftharpoons C_2$ where drug concentration C_1 is held constant over a time, Fick's law is $d(C_1 - C_2)/dT = -P(C_1 - C_2)$ (1)

Dividing both sides by C_1 we have,
 $(d(C_1 - C_2)/((C_1 - C_2)/C_1) = -PdT$ (2)

After integration one obtains,
 $\ln(C_1 - C_2)/C_1 = PT$ (3)

The constant of integration is 0, since when $T=0$, $C_2=0$ and $\ln(C_1 - C_2)/C_1 = 0$. P has the dimension of time⁻¹ and is physically defined as the Permeability Rate Constant.

If the diffusion of the drug across such systems obeys Fick's law, one gets a straight line with a -ve slope if IHS is plotted against T of Equation (3). Therefore the half life of drug (two kind of half lives will be obtained) $(C_1 \rightarrow C_2$ and $C_2 \rightarrow C_1$ in general) will be given by $T = 0.693/P$ (4)

In the present study the plasma lithium is assumed to be in a steady state after the 4th day of medication and plasma is consi-

dered C_1 and erythrocyte as compartment C_2 .

RESULTS

The result of Le and Lp values are plotted against time in Fig. 1. It shows that there is an almost steady state of Le and Lp levels remaining fairly within 1-1.2 mmols/L during the period of treatment. After discontinuation of lithium, Le levels fall slowly in a linear fashion whereas decay of Lp is non linear. From the plot of elimination, the plasma $T_{1/2}$ has been calculated at intervals of XY, YZ, ZO (fig. 1). It shows that the non linear plot yields $3T_{1/2}$ s (Table 1).

TABLE 1. Plasma $T_{1/2}$ s of lithium determined from the slopes of elimination of Lp (Fig. 1).

Time interval	Distance on the Lp elimination in Fig. 1	$T_{1/2}$ in Hrs.
15-18 days	.. x y	36
18-20 days	.. y z	24
20- z o	19

The figure also shows that from the 3rd day, the (MSRS) rating decreases upto 12th day and achieves minimal level on 10th day. Once the drug is discontinued on the 15th day, the rating goes up again. The nature of mood variation with drug does not seem to parallel either Le or Lp. As there has been a steady state lithium in one of the compartments, the same data points are subjected to fit the theoretical model for evaluation of $T_{1/2}$ from 3rd day to 15th day. The results of such kinetic analysis are tabulated (Table II) and plotted (Fig. 2).

TABLE 2. Lithium T_s determined from the kinetic plot. $T = 0.693/P$

Hours	θ	$\tan \theta$	$T_{1/2}$ c p hr.	$T_{1/2}$ pe hrs.
72-144	.. 3*	-0.0524	..	317.28
144-216	.. 67*	-2.3559	..	7.20
216-288	.. 39*	0.8098	20.40	..
288-360	.. 40*	-0.8391	..	19.68

FIG. 1
CONCENTRATION OF Li^+ IN PLASMA AND ERYTHROCYTES.

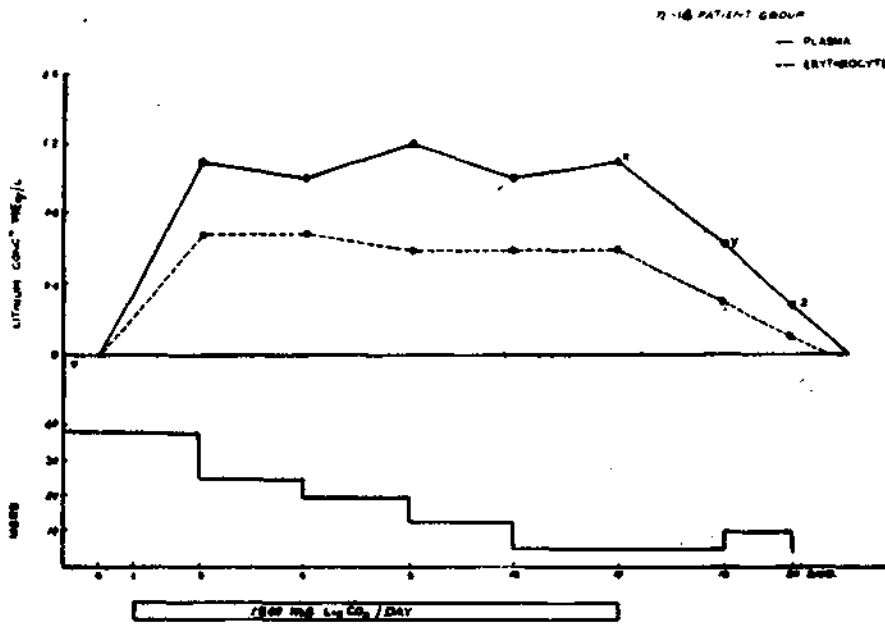
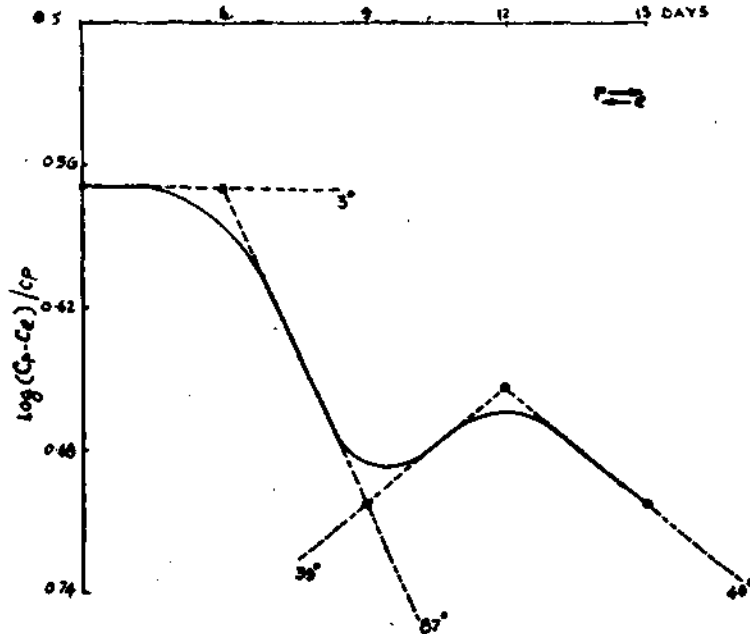


FIG. 2
FIGS. DIFFUSION MODEL FOR KINETICS OF Li^+



DISCUSSION

The present study shows that the decay of Lp is non linear in contrast to that of Le. Mendels and Frazer (1973) report that Le level is a better indicator of brain lithium concentration than Lp. The decay of Le parallels that of brain lithium whereas Lp has been shown to be non linear. Because of non linearity of the Lp decay, the calculation of plasma half life from the slope of elimination giving rise to a single $T_{\frac{1}{2}}$ becomes incorrect, unless the decay is exponential. Lyttkens *et al* (1976) have found the plasma half life in a range, 19 ± 1 for healthy females, 23 ± 1 for healthy males, 19 ± 2 for schizophrenic females and 21 ± 3 for schizophrenic males. In the present study, by taking 3 different points of observation in the line of elimination, 3 different half lives for plasma lithium have been calculated, as 36 hrs., and 19 hrs. It can be noted that the $T_{\frac{1}{2}}$ decreases over time for the same system.

The other half lives of serum lithium have been reported by Amdisen (1975). His values are based upon computerized regression analysis of a large population. He predicts 3 half lives : 35 hours (abnormal slow excretors) 20 hours (normal slow excretors) 8 hours (fast normal excretors). A wide range of inter individual differences of lithium clearance has been reported in literature and has been reviewed by Fyro and Sedvall (1975). The question of lithium retention has been the subject of a number of studies with inconsistent results. The investigations dealing with lithium retention, however in reality are reports on the fraction of an ingested lithium dose excreted in urine within a particular time period. Trautner *et al* (1955) have reported that healthy persons excreted 50-70% of the ingested dose in 24 hours whereas manics excreted only 13-19%. Gershon and Yuwiler (1960) noted that lithium excretion was 45-75% of the ingested dose in normals but was 12-17% in manics. One of Traut-

ner *et al* (1955) hypothesis is that manics have a positive lithium balance and undergo a negative balance during recovery has been tested by several studies. It has been supported by Hullin *et al* (1968) and Greenspan *et al* (1968). In part the argument against lithium retention has been overcome by demonstration of negative lithium balance on improvement from mania, by Greenspan *et al* (1968). The most recent study of Almy and Taylor (1973) also indicates lithium retention in mania. In the same line Serry's lithium retention test in predicting response to lithium in manics remains to be evaluated. Epstein *et al* (1965) and Platman *et al* (1968) have found no difference in lithium excretion between manic and non manic cases and the lithium excretion seems to be dependent upon sodium intake. Stokes *et al* (1972) have tested to replicate Serry's work. However, both Serry (1969) and Stokes *et al* (1972) have reported that several patients changed from retainer to excretor after successful lithium treatment. It points to the fact that lithium kinetics in manics is never uniform over time. In the present study it has been shown from the curve of elimination that Lp has 3 half lives (Fig. 1). It is difficult to dissect whether each patient is capable of exhibiting 3 different half lives or not. A kinetic analysis has been done with the same data points, fitting into Fick's diffusion law expressed as $\log (C_1 - C_2)/C_1 = -pT$, where $T = 0.693/p$, (Fig. 2). The results of the kinetic analysis (Table 2) shows 3 different categories of half lives too. It shows that from 3rd day to 6th day the patients excrete less of lithium with a half life 317.28 hours and it goes in favour of lithium retention supported by Greenspan *et al* (1968), Hullin *et al* (1968), Serry (1969) and Almy and Taylor (1973). In addition the kinetic plot for MDP cases shows that following retention, there occurs fast excretion half life-- 72 hours by 6th to 9th day, during which the clinical mani-

festations is on the peak of its decline. After the 9th day, lithium half life becomes 19.68—20.04 hours—slow normal excretor range of Amdisen (1975). It shows that lithium half life can vary in any direction in any magnitude over time. It has also been pointed out that the system can exhibit 3 or more different half lives over a period of time. (Pradhan et al, 1977). After discontinuation, the L_p level at no time is found below the L_e level. From the kinetic analysis it is evident that from 3rd to 15th day lithium distribution between plasma and erythrocyte goes through at least four steady states and yields three $T_{1/2}$ of which two are identical in either directions. Thus it is gratifying to note that kinetic plot not only reproduces original data $T_{1/2}$ s but also predicts another set of $T_{1/2}$ s showing the whole range lithium distribution over time.

Appendix : Estimation Procedure of plasma and erythrocyte lithium :

Heparinized blood 4 ml is (NH_1 heparin, Sigma product No. H-0880) centrifuged at 3500 r.p.m. for 5 minutes. The plasma is separated and L_p is determined by Coombs procedure (1971). The buffy coat containing leukocytes and platelets is discarded by aspiration. Then the erythrocyte portion is suspended in isotonic $MgCl_2$ (112 mmol/L) and centrifuged at 3500 r.p.m. for 5 min. and the supernatant is discarded. This washing procedure is repeated 3-4 times to get rid of trapped electrolytes of plasma. Each time after the wash the supernatant is examined for presence of sodium ion (flame photometry). 1 ml of the washed erythrocyte preparation is taken and haemolysed by addition of 9 ml deionised water (dil 1 : 10) for estimation of L_e . P.C.V. is determined for this erythrocyte preparation also. The L_e value calculated as

$$\text{Recorded value} \times \frac{100}{\text{P.C.V.}}$$

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