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Lithium Pharmacokinetics

Shortly after Cade (1949) observed the antimanic action of lithium (Li), it became apparent that clinically significant Li toxicity could develop and could be life threatening. At that time, many clinicians viewed Li as too toxic a drug to use, and it almost dropped from clinical usage. It was only when the clinical pharmacology was determined by monitoring the plasma Li levels for side effects that it became possible to use Li safely and effectively (Noack and Trautner, 1951; Shou et al., 1954; Trautner et al., 1955; Baastrup, 1971). In particular, plasma levels were important when Li was used for prophylactic purposes, where the end point of a response to an acute illness was absent.

Amdisen (1967) was the first to work out a standardized technique for monitoring plasma Li levels to aid in dosage adjustment. Morning Li levels on blood drawn before the first morning dose, roughly 12 hr after the evening dose, provided a standardization for the time of drawing samples. This work in the early 1960s on the practical pharmacokinetics of Li was used as an aid to dose adjustment and has since been a standard clinical practice. Recently, saliva Li and RBC Li have also been proposed to be helpful in monitoring Li treatment. In this report we will focus our discussion primarily on plasma Li.

Plasma Levels and Therapeutic Effects

Amdisen (1975) and Schou et al. (1968 and 1971) defined the cumulative dose response curve for long-term Li treatment based on their clinical experience. At present, data on plasma levels and therapeutic levels of Li using carefully controlled techniques have not been collected; however, clinical experience indicates that therapeutic levels are approximately 1 mEq/liter, and toxic levels begin in the neighborhood of 1.5–2 mEq/liter.

The appropriately designed study to test these findings requires treating patients with a fixed dose of Li for periods of weeks and correlating plasma levels with therapeutic efficacy when Li is used in the treatment of mania. A similar methodology would have to be used to define the relationship between plasma Li and side effects.

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Plasma Levels and Side Effects

It has been suggested that certain Li side effects (e.g., tremors, a mental feeling of being in a daze, nausea) have been suggested to be associated with Li peaks after an acute oral dose. Side effects occurring in patients receiving different pharmaceutical formulations of Li with different pharmacokinetic profiles can be compared. However, most of these studies do not provide definitive evidence. Indeed, the differences between certain pharmaceutical formulations of Li can be somewhat minor. Yet even minor differences in formulation can reduce side effects (Grof et al., 1976). Given the many variables that may govern side effects (e.g., individual differences and rate of Li absorption, fasting or nonfasting, the presence or absence of meals, imprecision in quantitating side effects, different susceptibility to side effects, differing thresholds of reporting side effects among patients), it is not surprising that some authors fail to report peak levels that correlate highly with such side effects as nausea and trembling (Fyro et al., 1970; Laurell and Persson, 1970; Persson, 1971 and 1974a and b; Edstrom and Persson, 1977).

Many authors have noted such side effects as tremors, dazed feelings, and nausea related to Li peaks (Amdisen, 1974b; Amdisen and Schou, 1967; Manissek and Hessling, 1971; Borg et al., 1974; Consbruch et al., 1978). Currently there are no studies that find that these side effects occur principally in the trough between the peaks. Thus, it seems that there is a preponderance of evidence suggesting a modest relationship to the peaks.

There are several parameters involved in the correlation of peaks to side effects after ingestion of a tablet of Li. These parameters include the dose given, the level (or trough) between peaks, the mean peak level, the maximum level of a peak, and the rate of rise from the basal level to the peak. Persson (1977b), in a particularly interesting study, quantitated these various parameters and correlated nausea and tremors to different parameters of the absorption peak. He administered Li at 8 AM and drew blood at 8:30, 9:00, and 10:00 AM. He quantitated the rate of rise by using the angle formed by a horizontal line and the intersecting line formed from the basal level to, for example, the 8:30 AM level. These measures can be made for each of the three time points, and the maximal angle can be calculated. This provides a measure of the rate of rise. Intercorrelations between these measurements reveal, in essence, two factors: one factor is the peak level in an absolute sense, and the other factor is the rate of rise. Persson found a significant relationship between tremors and nausea to both the peak level and the rate of rise. Although Persson did not use a multivariant method, it would have been possible using this method to try to separate out these two effects. The highest correlation to side effects was with peak levels. By holding this parameter constant, it would have been of interest to see if the rate of increase played an independent role, or if the correlation could be entirely accounted for by the peak level. It is also of interest that Persson found a negative relationship between loose bowel side effect and peak levels. None of these correlations were statistically significant, but they were consistently in the direction that found loose bowels with low peaks. We will return to this point later.

There has been some concern about Li toxicity to the kidney since Hestbech et al. (1977) pointed out that Li can produce a chronic interstitial nephritis. To put this concern in perspective, it is important to note that there is no evidence that supports an increase in mortality with Li over that which might be observed in a comparable control population (Glen et al., 1979), nor is there an excess of patients on Li who die of renal failure. There is a legitimate concern for the renal biopsy data, particularly since the findings have been replicated by six separate groups (Copper et al., 1979; Editorial, 1979). The real question in all these studies is whether the control groups were adequate (Copper et al., 1979; Kincaid-Smith 1979). Copper and his colleagues (1979) found that there was little difference in renal function

between a Li-treated group and a control group of affective patients untreated by Li. The possibility remains, however, that Li may cause chronic nephropathy. If this could be etiologically related to peak values of Li, then it would be particularly desirable to avoid high peak values in patients on Li through the use of sustained-release pharmaceutical formulations. Of interest here is the observation in 35 patients treated daily with Li that the maximum Li peak correlates positively ($r = 0.48$; $P < 0.01$) with the pH of the urine specimen: i.e., the first urine specimen after the Li dose (Mellerup et al., 1979). It should be pointed out, however, that, although it is reasonable to form the hypothesis that Li toxicity might be related to peak plasma levels, there is no convincing proof that this is the case. It is certainly conceivable that the opposite could be true, as Mellerup et al. (1979) point out. It may be that low plasma levels may be beneficial in allowing some sort of cellular regeneration process to occur. The relationship of Li to sodium or other ions could play a role (Baer et al., 1973; Mellerup et al., 1976; Petersen et al., 1974).

A once a day regime is more convenient than a three or four times a day regime. Much of the work relating peak Li levels to side effects is based on the assumption that it is better to avoid high peaks and low troughs in Li pharmacokinetics. The most important reason for this concern involves the effect Li has on the kidney. It is certainly reasonable to hypothesize, although it has not been proven, that high Li levels in the kidney might be particularly dangerous in terms of producing interstitial nephritis.

Thus, there are three advantages for a Li formulation that avoids extreme high peaks: (a) there is a slightly lower incidence of nausea and tremor; (b) there is better compliance owing to a simpler mode of administration (once or twice a day as opposed to three or four times a day); and (c) there is the potential for avoiding Li interstitial nephritis in the kidney. It should be emphasized that the third advantage is not proven, but is just a hypothesis. Yet, on the other hand, many authors have noted diarrhea occurring frequently when various slow-release Li formulations were utilized. We will discuss this in more detail later.

Lithium Absorption

This consideration has led to many studies of the pharmacokinetics of the Li absorption of different Li formulations. When Li is administered as a dilute solution, it is rapidly and completely absorbed. The majority of Li capsules or tablets available commercially are almost completely absorbed. Most studies find 80%–95% of the administered dose are recoverable in the urine. Lithium is absorbed throughout the gastrointestinal tract. This inference is supported by the observation that Li is well absorbed by rectal administration of suppositories and also by the use of entericoated tablets of various doses (Amdisen, 1974b). In general, it would be expected that there would be fewer side effects with sustained release tablets owing to the association of some side effects to the peak plasma levels (Marini and Sheard, 1976). However, there is increased diarrhea with some ultralong-acting sustained release Li preparations. In these ultraslow absorption preparations, sufficient Li reaches the large intestine to cause diarrhea. This clinical concern has resulted in much interest in the bioavailability of Li in various pharmaceutical formulations. Several of the early delayed-release formulations were not entirely satisfactory. Lithium was relatively poorly absorbed, but more importantly, absorption was also variable (Copper et al., 1969; Cooper et al, 1978; Otto et al., 1972; Tyrer et al., 1976; Amdisen, 1974b and 1975). Such bioavailability nonequivalence makes dosage particularly unpredictable. Diarrhea, which many patients experience 4 or 8 hr after taking the dose, occurred with an early Scandinavian formulation, Lithium Lipett C (ACO Lakemedel, Sweden) and also with an early British formulation, Priadel (Delandale; Persson 1974a and 1974b; Amdisen and Sjogren, 1968; Copper et al., 1969; Fyro et al., 1970; Persson, 1971).

The observation of a relatively lower bioavailability of the old formulation of Priadel (Copper et al., 1969) was verified by Amdisen (1975), who found 58.7% of the administered steady-state dose recovered in a 24-hr urine of patients. Caldwell et al. (1971) were able to calculate 100% bioavailability for a Li solution. Two acute Li preparations (Eskalith; Smith Kline & French; and an experimental preparation prepared by the Veterans Administration) yielded a bioavailability of 96% and 97%, respectively. However, the experimental delayed-release preparation was only 58% bioavailable. A single dose pharmacokinetic study was performed by Tyrer and his co-workers (1976) using three preparations: (a) a newer formulation of Priadel, (b) the British lithium capsule, Camcolit (Norging), and (3) a British sustained release preparation, Phasal (Pharmax); using single dose pharmacokinetics Priadel, which was quite similar to Camcolit, the differences found were rather minor. Substantially lower amounts of Phasal was absorbed during the first 24 hr than from either of the other two preparations. Furthermore, substantial amounts of Phasal (35% ± 12%) was recovered in the feces over time periods of 27–56 hr. Substantial lower amounts of Camcolit (6% ± 2%) and Priadel (4% ± 1%) were recovered in feces collected over somewhat longer time periods.

Bennie et al. (1977) did a steady-state bioavailability study on three Li preparations: Camcolit (Camden Chemical Company), lithium carbonate tablets, and a sustained release preparation (Priadel and Phasal). They compared the two sustained release preparations to Li capsules administered three times a day and Li capsules administered once a day using plasma levels drawn at steady state. Plasma levels were clinically adequate, i.e., within the therapeutic range of 0.6 to 1.2 mEq/liter for Camcolit administered three times a day, or the two sustained release preparations administered once a day. There was, however, a higher peak and bigger troughs after the administration of Camcolit tablets once a day. In thinking about pharmacokinetics, it is important to recognize that the pharmacokinetic profile in the steady-state condition is the appropriate parameter in comparing different preparations, rather than single dose pharmacokinetics. Single dose, as well as multiple dose pharmacokinetics, is important in understanding the pharmacokinetics of the drug, but the ultimate concern is what happens during steady state. Inspection of the data of Bennie and co-workers (1977) revealed that plasma levels of the so-called sustained release capsules were relatively high for roughly 12 hr, but did drop substantially into a trough by 20–24 hr. To have trough levels of around 0.6 mEq/liter it was necessary that peak levels be between 0.8 and 1.0 mEq/liter for Priadel. The ratio of peak values to trough values for Priadel in comparison with the Camcolit tablet is quite similar. It is of interest that the standard deviation of plasma levels under the steady-state condition of patients receiving Priadel was much smaller in patients receiving Phasel.

Amdisen (1974a and b) studied the recovery of Li in the urine of subjects on a steady-state dose and found the bioavailability of different formulations as follows: lithium citrate tablets, 85%; lithium carbonate tablet, 88%; sustained release tablets (Lithionit), 90%; Priadel old formulation, 59%; Priadel new formulation, 87%, and sustained release tablet Litarex 88%.

Grof et al. (1976) did multiple dose pharmacokinetic studies of these preparations: (a) a Canadian lithium carbonate capsule containing pure lithium (carbolith; Winley Morris, ICN), (b) Lithizine (Paul Maney): lithium carbonate with additives, a preparation that shows a slight degree of slower release than lithium carbonate capsules or tablets, and (c) the British preparation, Priadel. It is of interest that there were no significant differences in bioavailability between all three products. Twenty-four-hour urinary recovery of Li was 82.4%, 90.7%, and 98.5%. However, the slow-release formulations had slightly less side effects than lithium carbonate, although the pharmacokinetic properties of the Priadel provide an almost negligible degree of slow release (Tyrer et al., 1976). It does not seem to produce a decrement of side effects. Crammer et al. (1974) did find Priadel to have a slightly slower absorption than is usually seen with the lithium nonslow release formulation. Sugita et al. (1973) found the Paul

Maney formulation to be slightly slower in absorption than lithium carbonate capsules (Eskalith; Smith Kline & French).

Griel and his co-workers (1976) studied the pharmacokinetics of lithium acetate and lithium aspartate. Plasma levels of lithium aspartate were substantially lower than those observed with lithium acetate. After oral administration, there was a lag period of several hours before Li plasma levels rose. Lithium acetate peak levels occurred at 1–2 hr, whereas lithium aspartate peak levels occurred at about 6 hr. Studies of recovery of Li in the urine indicated that substantially less amounts of Li given in the aspartate form were recovered in the urine over an 8-day period after a single oral dose. Lithium acetate and lithium aspartate were administered i.v., and blood was collected initially every 15 sec. Plasma levels of Li were virtually identical when these two forms were given. Similarly, after i.v. administration, recovery of lithium aspartate in the urine was very similar to that of the recovery of lithium acetate. The i.v. studies indicate that the pharmacokinetics of the Li administered in these two forms is practically identical. It is reasonable to assume, therefore, that the lower plasma levels and lower recovery of Li from the urine when Li is given as lithium aspartate, are a result of incomplete absorption.

Thornhill (1978) compared ordinary and sustained lithium carbonate (Quilonum Retard) administered to both acute and chronic patients. He fitted the data from both preparations to a model yielding absorption, redistribution, and elimination mean half-life of 0.78, 5.06, 27, and 3.7, 4.4, and 26 hr for the ordinary and sustained release forms, respectively. The area under the curve (AUC) of the sustained release preparation was 85% of that of the ordinary preparation, indicating a slight lower bioavailability, a result consistent with the other studies of slow release preparations. The author notes that adequate serum levels can be obtained with the sustained release form administered twice a day and with the ordinary preparation given three times a day.

Altamura et al. (1977) found little difference between pharmacokinetic parameters such as the AUC, half-life, total body clearance, and the apparent volume of distribution between the various salts of Li (lithium carbonate, sulfate and chloride).

Diarrhea and Slow Release Formulations

Persson (1974a) also noted diarrhea after the slow release sulfate preparation with lithium Lipett C. Others have also reported diarrhea with slow release formulation (Fyro et al., 1970; Borg et al., 1974; Laurell and Persson, 1970).

Persson (1974b) did a multiple dose pharmacokinetic study and suggested that this slow release formulation had slightly less bioavailability than carbonate tablets, but a lower peak value. To avoid the diarrhea, a newer "medium release" formulation of lithium sulfate (Lithionit Durretter) was compared with an older version (slow release) of this formulation, as well as to a coated lithium carbonate tablet (some patients find ordinary lithium carbonate tablets to have an unpleasant taste). In a systematic study of side effects, there were few differences in the side effects between medium release formulation and the coated Li tablets. A higher frequency of diarrhea was found with the slow release tablets (Edstrom and Persson, 1977).

Jepsson and Sjogren (1975) did single dose studies in normal volunteers ($n = 30$) comparing the occurrence of diarrhea in patients administered the slow release Li formulation (Lithionit; Durretter and Litarex) given either in a fasting state or immediately after meals. Virtually all the cases of diarrhea occurred with slow-release Li given to fasting subjects. Urine was collected in 10 subjects given Lithionit Durretter for 120 hr, and the percent recovered from fasting and

nonfasting subjects were 79% ± 3% and 92% ± 2%. It would seem that when fasting tablets pass rapidly through the intestinal tract yielding high Li concentration in the large intestine, hence, there is diarrhea plus a less complete absorption with more than 21% as opposed to 8% not being absorbed and presumably appearing in the stool. It seems that a simple factor such as whether Li tablets are taken with meals or during a fasting state has important implications for Li pharmacokinetics and side effects.

It is of interest that Persson (1977a and b) found a consistent pattern of a negative relationship between peak height and loose stools, and, although none of these differences were statistically significant, the findings were consistent in terms of the direction, and suggest that individual differences in the pharmacokinetic profiles of different subjects on the same lithium carbonate tablet reflect Li's effect on the large intestine. Diarrhea is not a medically intricate or life-threatening side effect, but it can be a nuisance and is important to some patients. It would seem desirable to use medium duration formulations of Li to avoid excess amounts of Li reaching the large intestines and causing diarrhea and incomplete absorption.

Discussion of Bioavailability Studies

The assumption underlying the thinking of some authors' work on Li bioavailability is that a reduction in bioavailability is clearly "bad." This may not necessarily be true. It could be that a preparation of Li that was 70% bioavailable, but that had uniform absorption, no high initial peaks, and did not cause diarrhea, might be perfectly suitable. It is important that the bioavailability be known because if a product with a lower bioavailability is used, the clinician must adjust the dose slightly higher. Of course, each patient receives a different dose depending on plasma level, side effects, and therapeutic effects, so the clinician needs to know the differences in the range of Li doses. The critical problem that arises with drugs that are incompletely absorbed is that one patient may absorb less than another patient. For example in the study of fecal Li levels of Tyrer et al. (1976), there were marked differences in the fecal excretion of Li. One patient had 82% of the administered dose recovered in the feces while another patient had as little as 7% recovered in the feces. This would suggest that the former patient absorbed only 18% of the dose while the latter patient absorbed 93% of the dose. Such variability in absorption between different patients receiving this particular formulation could be a problem clinically. It would obviously be important to note that variability in absorption is as important a parameter as the mean bioavailability of the preparation. We emphasize this because the former is often emphasized at the expense of the latter.

Consbruch et al. (1978) found that in patients receiving the slow release lithium sulfate formulation (lithium Duriles) 98% of the dose could be recovered in the urine. Bergner et al. (1973), using an experimental slow release formulation (Rowell laboratories, USA) compared to the standard lithium carbonate tablet (Lithotabs), found that 68% of the slow release dose was recovered in the urine in the first 48 hr while 80% of the lithotabs were recovered at the same time point. Single dose pharmacokinetics may provide only an approximation of absorption unless studies can determine accurately the excretion tail to an accurate approximation of infinity. Slow absorption can artifactually increase the beta phase $t_{1/2}$. Inaccuracies in measurement of the tail of the area under the time curve can alter the results and do so particularly if the curve is interpolated to infinity as a single exponential: i.e., a small error of measurement can effect the calculation. Note, Cooper et al. (1978) recovered 99% of the dose in the urine of the slow release formulation during steady-state conditions. Steady-state, plasma levels drawn in the standard manner were significantly ($P = 0.02$, Student's t-test) higher with the

slow release preparation given twice a day as opposed to the standard tablets administered two or three times a day to the same patient.

Pharmacokinetic Models

Several authors have fitted plasma level data to the two-compartment model with absorption after first-order kinetics. Caldwell et al. (1971) and Poust et al. (1976) showed a good fit for some, but not all patients using this model. Poust et al. (1976) extended their work by performing a pharmacokinetics single dose study of 4 normal volunteers where Li was given in the presence and in the absence of chlorothiazide. He found that the thiazide increased plasma levels by 26% and decreased Li clearance by 26.5%. Pharmacokinetic analysis showed that the thiazides produced change in renal clearance. This change was accounted for by the 24% reduction in the value of K_e, the excretion rate constant. The good fit to the two-compartments open model absorption after first-order kinetics is particularly useful in that it may allow predictions about Li pharmacokinetics in steady state. Indeed, this group compared predictions from the single dose pharmacokinetcs with Li values observed in patients at steady-state levels and found a good correspondence in 3 patients (Poust et al., 1976). Similar methods have been used by Groth et al (1974) and Amdisen (1975, 1977).

Griel and his co-workers (1976) administered Li i.v. and fitted the observed plasma levels to a four-compartment model. Plasma levels dropped rapidly in the first few minutes after injection, and then to a slightly slower rate for the next 2.5 hr or so. Then at a still slower rate from 3 hr to approximately 9 hr after injection, and ultimately in a still slower fourth phase 9 hr–30 hr.

Volume of Distribution

Amdisen (1975, 1977) found the apparent volume of distribution calculated by fractional urine collection made during the first 16 hr to be about 50%–90% of the body weight. Lehmann and Merten (1974) found a slightly higher volume in young people (1.2 liter/kg or 120%) than in older people (90%). Groth et al. (1974) measured the apparent volume of distribution in single dose pharmacokinetics calculating an absorptive phase and a fast and slow phase of excretion half-life. They estimated an apparent volume of distribution from the formula ($V_a = D \times F/A \times B$, where D = dose, F = fractions absorbed, assumed to be 100% here, A = area under the curve, and B = beta elimination constant). The volume of distribution so calculated, varied from 0.65 liter/kg to 0.85 liter/kg.

Mason and his co-workers (1978) administered Li chronically for steady-state studies in schizophrenics who were also receiving antipsychotics and other drugs. Plasma Li (steady state) was measured 12 hr after the first dose and then daily for 4 days. A one-compartment, open model for these conditions was assumed, and the apparent volume of distribution and other parameters were calculated. The former parameter ranged from 0.39 to 1.39 liter/kg (mean + standard deviation = 0.79 + 0.34 liter/kg). All authors found substantial individual variations in the apparent volume of distribution.

Excretion

Lithium is almost entirely excreted in the kidney. Indeed, when Li is administered in solution, virtually 100% is recovered in the urine. Renal Li clearance is in the range of 10–40 ml/min in normal patients (Amdisen, 1977). Renal Li clearance is calculated from normal subjects after the intake of a single dosage of 24 mMl, fractional urines being collected during the first

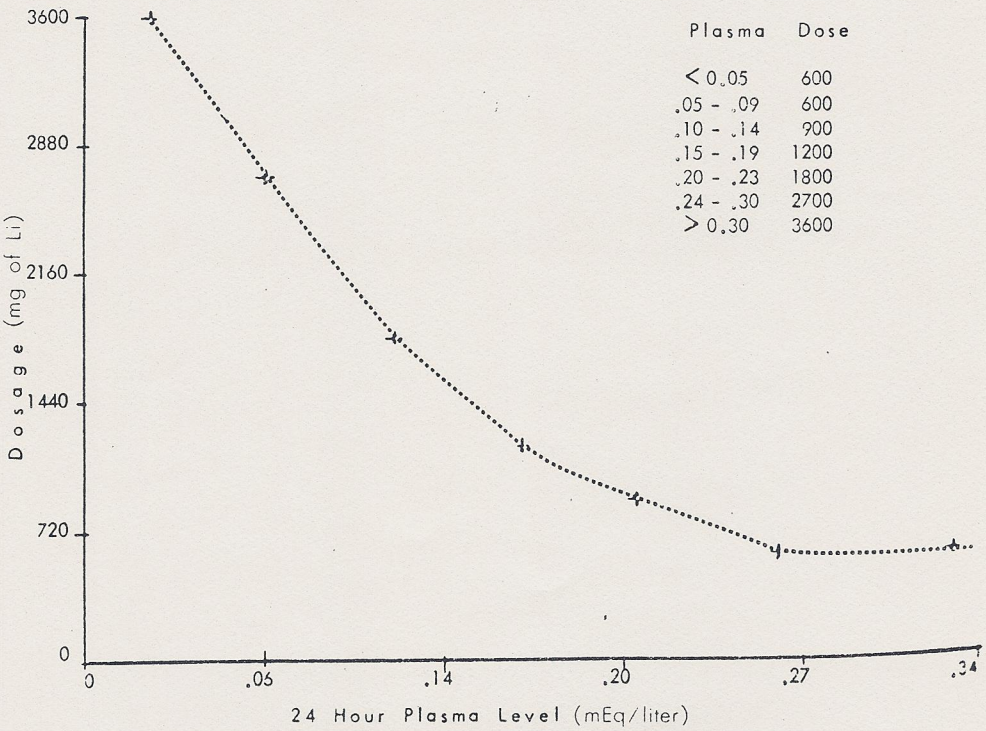
16 min after intake. Fyro et al., (1973) found creatinine clearance corrected significantly with Li clearance ($r = 0.65$). Although the relationship of Li pharmacokinetics to salt intake is beyond the scope of this review, it is important to remember that conditions that alter salt, such as a low salt diet, diuretics, pregnancy, fever, exercise, extremely hot days with excess sweating, and the administration of exogenous salt, can alter the Li balance (Thomsen and Schou, 1968; Peterson et al., 1974; Schou et al., 1973).

Lithium clearance can vary substantially from higher clearance during the day to lower clearance during the night. Indeed, $t_{1/2}$ of Li can be as much as 2.5 times longer during the night as during the day (Amdisen, 1975). Several workers using two-compartment, open models after oral Li administration estimate an elimination half-life in the range of 3–11 hr (Caldwell et al., 1971; Groth et al., 1974; Poust et al., 1976). This is consistent with the data of Amdisen (1975) who found most values between 7 and 21 hr in 177 patients and 49 healthy subjects (range 4–42). This was calculated from plasma levels drawn between 14 and 22 hr after the first single dose. Most healthy patients have a somewhat faster half-life than the conventional 24 hr half-life of Li so often reported in the literature. The histograms of Li half-lives show most patients have between 7 and 21 hr, but a minority of patients who have impaired renal excretion have half lives of 21–42 hr.

Prediction of Optimal Lithium Dosage

One of the major tasks in Li treatment is to adjust the dosage so that optimal therapeutic plasma concentration can be obtained as quick as possible. It is, therefore, of clinical importance to predict optimal dosage of Li in each patient at the beginning of treatment.

Figure 1. Prediction of dose necessary to achieve steady-state plasma level obtained after test dose *(Data from Cooper et al., 1973).*



Several authors have reported prediction methods using Li renal clearance (Schou et al., 1970) or plasma concentrate curves after an initial testing dose (Bergner et al., 1973). These approaches involved complicated procedures and are not practical for clinical application.

Cooper and co-workers (1973 and 1976) administered a single dose of 600 mg of Li and drew blood 24 hr after this test dose. Patients were then treated with 600 mg of Li t.i.d., and steady-state Li levels were measured. The 24 hr serum Li correlated with the steady-state values after 600 mg t.i.d. ($r = 0.97$). The authors then proposed a predicted dose regime that they are certain to lead to serum levels of 0.6 to 1.2 mEq/liter. Cooper et al. (1973) presented a table (see our Figure 1) listing the 24-hr serum value after the 600 mg and the dosage regime that they assert will lead to the appropriate serum level. However, this group failed to indicate how they went from the empirical data to their recommended dosage. Their data is based on the correlation of the plasma levels after a test dose with steady-state levels after a constant dose. Thus, they attempted to determine a prediction dose that yields a given standard steady-state level from a plasma level after a test dose. There are many possible rationalizations for constructing a table of recommended dosage based on these test dose values. Their prediction scheme is presented in graphic form in Figure 1. It is reasonable to have a clear-cut rationale that can be explicitly stated in order to explicate the reasoning underlying such predictions. This problem is compounded by the stated equation of Bergner et al. 1973, which predicts a much higher Li level than we expected at the 12-hr standard sample. Indeed, we think their prediction should be close to the peak. Seifert et al. (1975) administered slow release lithium carbonate Quilonum Retard in order to achieve a steady-state level of 0.9 mEq/

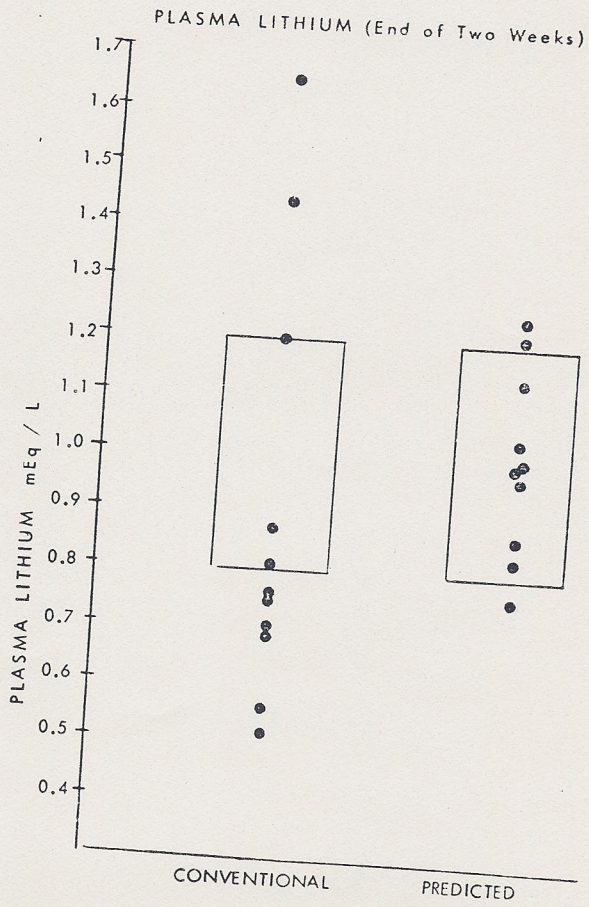


Figure 2. Comparison of plasma levels obtained using conventional methods for adjusting lithium dose vs. levels obtained when dose was adjusted via predictive method described in text.

liter for plasma drawn in the standard manner, i.e., the 12-hr standard technique. They administered a test dose of two 450 mg tablets and drew blood 24 hr later. From this, they predicted the number of tablets of this formulation given clinically to produce plasma levels of 0.9 mEq/liter. The formula was "the number of tablets = $4.61 - 5.67 \times$ test plasma level." The correlation between the number of tablets and 24-hr test dose value was 0.80. Chang and his co-workers (1978) administered a test dose of 900 mg given as 300-mg Li tablets and drew blood for single dose pharmacokinetics. This group found good correlations between the AUC, and the 12-hr and 24-hr plasma levels observed. Patients were then treated with Li in the normal clinical fashion, and plasma levels were adjusted to 12-hr standard steady-state levels of approximately 1.0 mEq/liter. Good correlations were observed between all parameters and this dose.

Using this method, Chang et al. (1979) reported 10 patients had their dosage requirements predicted at the beginning of Li treatment, and another 11 patients had their dosage adjusted by conventional trial and error methods to see whether this prediction method can actually achieve optimal plasma Li more accurately and faster than the conventional method. Both groups were aiming at obtaining a plasma Li of 1.0 mEq/liter. At the end of 2 wk, most of the patients given predicted dosage showed the plasma Li between 0.8 and 1.2 mEq/liter,

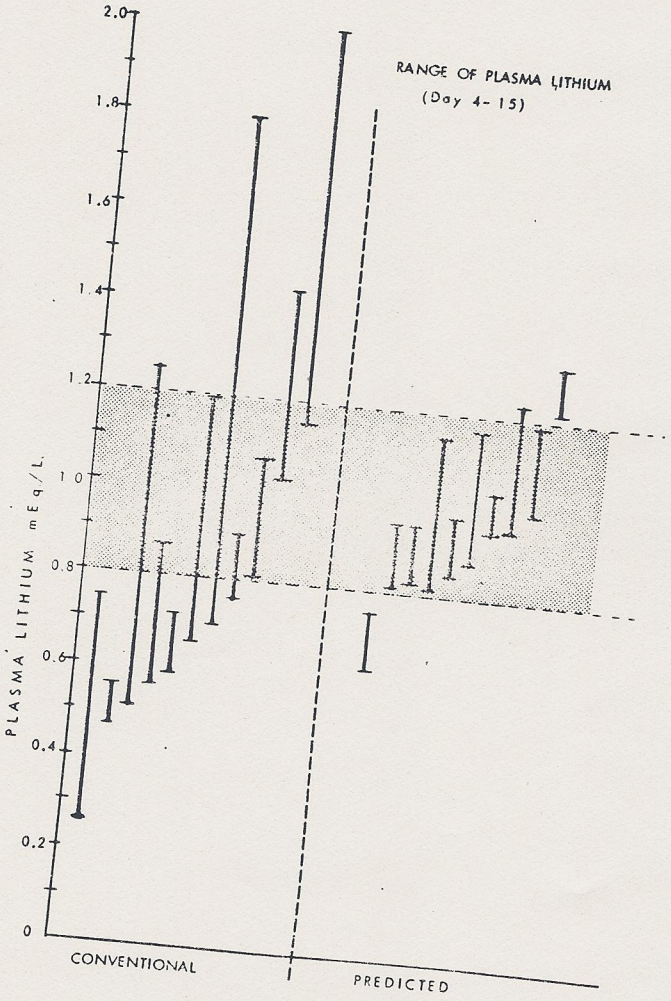


Figure 3. Range of plasma lithium levels obtained using conventional methods for adjusting lithium dose vs. levels obtained using predictive method.

which is very close to the prediction (Figure 2). During the course of a 2-wk Li treatment, the patients with conventional dosage adjustment showed a much wider range of plasma lithiums when compared with those patients who were on the predicted dosage (Figure 3). This indicated that patients with conventional dosage adjustment would be exposed much more often to the toxic or ineffective plasma Li. Although several workers (Cooper et al., 1973; Seifert et al., 1975; Chang et al., 1978 and 1979) found a good correlation between the test dose and steady state, the prediction study reported here is the first report where the actual dosage predicted by such an equation does, in fact, yield the desired plasma levels. With respect to this issue, Cooper et al. (1976) did not perform a controlled study to see if the prediction recommendations did, in fact, yield the expected result, but only asserted that they have used it in private practice.

General Remarks

This work deals only with plasma levels. Erythrocytes, saliva levels, or brain levels are not covered by this paper (cf. Frazer et al., 1973). There is a need in the U.S. for both a good medium-rate release preparation that avoids high peaks, and an ultra-slow release that can be administered b.i.d. We emphasize that the underlying assumption is the avoidance of peaks to lessen tremors, nausea, and possibly kidney damage. More work is needed for the optimal prediction formula from the test dose. There seems to be a linear relationship between plasma level and dose (Amdisen 1974b and 1975) so that a 5-day plasma level would allow a proportionate dose adjustment: i.e., we would expect plasma levels to be directly proportional to dose. We advocate dose adjustment to side effects and clinical response after the lag period. The usefulness of the test dose prediction and the 5-day prediction is to move quickly and accurately to obtain the plasma level within the usual therapeutic range. After that, the dose can be further refined by side effect and therapeutic response feedback.

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