The Ups and Downs of Oral Lithium Dosing

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As a mood-stabilizing agent, lithium has a long history of documented efficacy as well as risks associated with its use. Relative to other psychiatric medications, lithium exhibits a number of unique pharmacokinetic properties. The use of in vivo nuclear magnetic resonance spectroscopy of the ^{7}Li isotope has immense potential to provide an improved understanding of the pharmacokinetic basis of lithium response and nonresponse. The conventional use of orally administered immediate-release preparations of lithium salts in psychiatry is associated with high postabsorptive blood lithium concentrations and trough lithium concentrations in later phases of lithium elimination. These ups and downs of blood lithium concentrations are associated with acute lithium toxicity and symptomatic states, respectively. The use of slow-release lithium formulations represents a long available means of diminishing the postdose variation in serum lithium concentrations. A significant need exists for head-to-head comparisons of the pharmacokinetics and clinical response relationships for slow-release and immediate-release lithium formulations. *(J Clin Psychiatry 1998;59[suppl 6]:21–26)*

Lithium is the lightest of the alkali metals (group 1A) found in the periodic table of the elements (Figure 1). Lithium is also the first-line treatment for the management of acute mania and the prophylaxis of bipolar disorder. The specific effects of lithium on neuronal function in the brain that underlie its psychopharmacology remain unidentified. Lithium has no known physiologic effects in humans and no discernible psychotropic effects in normal humans. Of the many unique properties of lithium that underlie its valuable psychopharmacologic effects—physicochemical, pharmacodynamic—this article will focus on the pharmacokinetic properties of lithium after oral dosing. Particular emphasis will be placed on the influence of its pharmacokinetics or the benefit/risk ratios associated with its clinical use.

Lithium remains a drug for which its many and obvious benefits to psychiatry are offset by risks related to its well-documented organ toxicity. Lithium has the narrowest gap between the therapeutic and toxic concentrations of any drug routinely prescribed in psychiatric medicine and is poorly tolerated in one third or more of treated patients. The nearly 5 decades of clinical experience with the use of lithium in psychiatry is replete with evidence supporting toxic effects of lithium on the function of the brain, thyroid, kidney, and heart. The potential toxicity of the unmonitored use of lithium was well demonstrated by the fatal consequences of the ill-advised substitution of lithium chloride for table salt in the 1940s.[1] A review of the incidence of side effects and toxicity in 1094 patients treated with lithium revealed that 35% to 93% complained of adverse events related to lithium treatment.[2] A long recognized challenge to the effective use of lithium in the therapy of psychiatric illness is the high rate of drug noncompliance due to side effect complaints reported by patients. For example, only one third of patients in a recent community sample[3] were estimated to be compliant in their prescribed lithium dosing regimen. The mechanisms underlying the deleterious side effects of lithium are currently best explained by the complex actions of lithium ions on monoamine, amino acid, and neuropeptide neurotransmitters at both presynaptic sites and postsynaptic receptor signal transduction mechanisms in the brain and peripheral organs.[4] The incidence and severity of toxicity associated with lithium administration are related to the blood plasma concentration of lithium ions, and therapeutic drug monitoring techniques have improved the safe use of lithium.[5] While lithium is clearly of immense value in the management of the morbidity and mortality of mood disorders, the current problems related to lithium dosing may perhaps be best understood by a discussion of the routes and mechanisms of elimination of lithium after its oral administration. The intent of this discussion is to highlight the shortcomings of oral dosing as a routine route of lithium administration.

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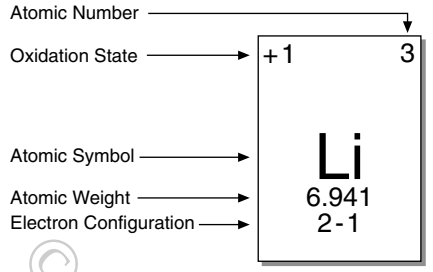
Figure 1. The Properties of Lithium as a Member of the Periodic Table of the Elements



THE FATE OF LITHIUM AFTER ITS ORAL ADMINISTRATION

Its pharmacologic activity resides in the lithium ion, and for reasons of solubility and formulation, lithium is orally dosed as lithium salts available in pill, capsule, and syrup formulations. Currently available rapid- or immediate-release dosage forms include lithium carbonate in pill and capsule forms and lithium citrate syrup. Lithium ions constitute only 10% to 20% of the mg doses of these salt formulations (e.g., 300 mg of lithium carbonate contains 56 mg of lithium).

A complete dissociation of the lithium salts into their ions occurs after oral administration of immediate-release formulations. Lithium is readily and virtually completely absorbed from the intestinal tract by passive diffusion through pores in the small intestinal membrane. A small fraction of the oral dose is transported actively in exchange for sodium. Complete absorption into the systemic circulation occurs within 8 hours. The direct exposure of the gastrointestinal system to lithium ions during systemic absorption is associated with gastrointestinal-related side effects including nausea and diarrhea. These effects are sometimes exacerbated by the increased gastrointestinal residence time associated with the dosing of sustained-released formulations. Lithium is found as a trace element in the human body; the typical blood plasma concentration is 15 to 20 μg/L (~2.5 μEq/L).[6] After the oral administration of immediate-release formulations, plasma lithium concentrations attain maximal values of 2 to 4 mEq/L or 1000-fold greater than typical trace concentrations.

From the systemic circulation, lithium is initially distributed in the extracellular fluid and then accumulates to various degrees in different organs. Beginning with this distribution phase, lithium distinguishes itself in its pharmacokinetics from other psychotherapeutic agents (Table 1). This is reflected in a final volume of distribution of lithium of 0.7 to 0.9 L/kg, a value similar to that of the total body water volume. Depending on their acid-base properties, virtually all other psychiatric drugs distribute in the circulation highly bound (> 70%) to serum proteins such as acid glycoproteins or albumin. Lithium exhibits

Table 1. Unique Pharmacokinetic Properties of Lithium

Negligible binding to plasma proteins
Does not undergo biotransformation; no first-pass effect
Virtually exclusive renal elimination
Drug interactions with lithium related to alterations in sodium balance

negligible binding to plasma proteins, and thus a significant mechanism of drug-drug interaction for some agents (e.g., valproic acid) is not exhibited for lithium. Lithium concentrations at steady state in the systemic circulation are approximately twice that found in red blood cells, muscle, and cerebrospinal fluid and similar to values found in heart and lung tissue.[7] The activity of sodium-lithium countertransport mechanisms in red blood cells, and perhaps muscle, presumably underlies the disproportionately low lithium concentration relative to plasma in these tissues.

The remarkable ability of the human body to eliminate drugs, toxins, and xenobiotics, often involving their complex biotransformation to more polar, readily eliminated metabolites, represents an effective barrier to intoxication. A major first-line of defense against the effects of orally administered drugs is represented by their high degree of extraction into the hepatic portal circulation. This route renders drugs readily available to the hepatic drug metabolizing systems that underlie the first-pass effect. An additional unique pharmacokinetic property of lithium relative to other psychotherapeutic agents is that lithium is not metabolized nor biotransformed in any appreciable way. Lithium, in turn, has negligible effects on the activity of the major hepatic drug metabolizing enzymes (e.g., cytochrome P450). Drug-drug interactions at this level, an increasingly recognized concern for many psychiatric drugs,[8] do not limit lithium use. The task of lithium elimination from the body falls to the kidneys. Lithium ions readily pass into the glomerular filtrate, with approximately 80% of the filtered load of lithium reabsorbed in the proximal renal tubules. The fate of lithium in the body is closely tied to that of sodium and, to a lesser extent, potassium. Although the lightest of the alkali metals, lithium has the highest energy of hydration, and its hydrated ionic radius (~310 pm) is similar to that of sodium with its hydration coat (340 pm). This similarity in ionic radius allows lithium to substitute for sodium in many of the active sodium transport mechanisms characteristic of biological systems. Perhaps the best example of this ability of lithium to substitute for sodium in ion transport is in the proximal renal tubules where lithium is reabsorbed in tandem with sodium. This close association of lithium with sodium homeostasis underlies the fact that drug interactions with lithium relate largely to alterations in sodium balance and renal states.[7] Many cases of inadvertent lithium intoxication can be readily understood in a context of alterations in the filtered load of sodium (e.g., hyponatremia), age, or

Table 2. Brain Lithium Concentrations in Mood Disorders: ^{7}Li Magnetic Resonance Spectroscopy

Delayed uptake and elimination relative to the blood compartment
C_{max} for brain Li^+ concentration occurs 0–2 hours after C_{max} for serum concentration[10]
Brain $t_{1/2}$ of 28 hours versus serum $t_{1/2}$ of 16 hours
Variably related to blood Li^+ concentration and daily dose
Brain/serum Li^+ concentration ratios of 0.4–1.0 at steady state[12,13]
Ratios fluctuate from 0.5–1.3 over a 48-hour period[14]
Moderate (r = 0.4–0.68) correlation of brain to serum Li^+ concentration
Lack of correlation to "therapeutic" serum Li^+ concentrations[15]
Significant correlation with daily Li^+ dose following long-term (> 6 months), but not short-term (4–8 weeks) administration[16]
Substantial interindividual differences in brain Li^+ concentration (0.5–0.87 mEq/L) at similar serum Li^+ concentrations[11]
Related to clinical state
Clinical improvement correlated with brain Li^+ concentration[12]
Response threshold of 0.2–0.3 mEq/L[17]
Mania associated with increased brain Li^+ concentration[18]

pathophysiologic or drug-induced decreases in renal function resulting in impaired renal clearance of lithium.

IN VIVO LITHIUM DETERMINATIONS IN THE HUMAN BRAIN

Brain imaging techniques offer new inroads into the human pharmacokinetics of lithium and the basis of lithium response and nonresponse. Lithium has two naturally occurring isotopes, ^{6}Li and ^{7}Li. In vivo nuclear magnetic resonance spectroscopy (MRS) of the ^{7}Li isotope after lithium administration to humans has recently been used to characterize the disposition of lithium after oral dosing.[9,10] Gonzalez et al.[11] described a ^{7}Li MRS method with optimized temporal and spatial resolution for the in vivo quantification of human brain lithium. The sensitivity and specificity of ^{7}Li signals were improved by the sampling of a standardized brain volume and more certain estimations of T_1 and T_2 relaxations for ^{7}Li. Use of these and related MRS techniques have furnished previously unattainable information related to the multicompartmental distribution of lithium following oral dosing and the perhaps unique relationship of brain lithium concentrations to clinical response (Table 2). Relative to serum lithium concentrations, brain lithium concentrations exhibit later peaks and slower rates of elimination. Brain/serum lithium concentration ratios, after both acute doses and at steady state, typically are less than 1.0. The capillary endothelial specializations forming the blood/brain barrier may buffer the brain lithium concentrations relative to the high postabsorptive circulatory concentrations of lithium. Brain lithium concentrations exhibit at best only moderate correlations with serum values, and bipolar patients with comparable serum lithium concentrations exhibit substantial individual differences. Interestingly, in at least one study,[12] brain lithium concentrations exhibited a better correlation with clinical improvement in the treatment of mania than did serum lithium concentrations. Moreover, the results from monitoring a single bipolar patient during the switch from a depressive to a manic episode suggested that mania may be associated with an increased brain lithium concentration.[18]

The use of in vivo ^{7}Li MRS may provide in differential brain lithium concentrations an ability to discriminate lithium responders from nonresponders. The results from a study of a small sample of lithium-treated bipolar patients did not, however, note a difference in brain lithium concentrations between lithium responders and nonresponders.[13] The relationship between brain lithium concentration and therapeutic and toxic drug effects remains largely unexplored with this exciting new technique. The potential advantages of different lithium dosing strategies (e.g., immediate- versus slow-release formulations) could be perhaps established using in vivo quantitative ^{7}Li MRS. Increases in the spatial resolution of brain MRS imaging techniques will enable a determination of the clinical significance of brain regional variations in ^{7}Li concentration suggested by postmortem studies.[19] MRS facilities with multinuclear imaging capability will provide increasing novel insights into the pharmacokinetics and neuropharmacology of lithium in the living human brain.[20]

UPS AND DOWNS OF ORAL LITHIUM DOSING

It is perhaps important to distinguish between acute postdose lithium toxicity associated with therapeutic dosing and cumulative toxicity associated with lithium intoxication. A recognized limitation of lithium use and patient compliance is the transient toxicosis associated with the postabsorptive peaks in blood lithium concentrations and their temporal characteristics.[21] Of interest to this discussion is accumulated evidence indicating that lithium toxicity is related to this maximal plasma concentration (C_{max}) as well as its rate of rise after oral administration.[21–23] The specific adverse events of nausea and poor concentration ability[24] and thirst and fine tremor[22] appear to be correlated in time or magnitude to the C_{max} obtained after oral dosing with immediate-release lithium preparations. A further limitation of the use of these formulations by an oral route is the occurrence of breakthrough manic symptoms associated with the trough serum lithium concentrations occurring in later stages of drug elimination. The relationship of adverse events and symptomatic states associated with the postdose peaks and troughs in serum lithium concentration can be considered as the ups and downs of oral dosing with immediate-release lithium preparations. These ups and downs represent significant limitations to the drug-taking compliance of patients with bipolar illness. A number of strategies, alone and in combination, have been implemented to circumvent these limitations of oral lithium dosing (Table 3).

Table 3. Strategies to Avoid Adverse Effects of Ups and Downs of Oral Lithium Administration

Therapeutic drug monitoring
Divided daily doses
Sustained-release preparations

Therapeutic Drug Monitoring

With accumulating evidence supporting wide interindividual variations in drug pharmacokinetics, particularly relating to drug metabolism and elimination, the concept of deriving an estimate of the individual pattern of drug disposition to guide dose adjustments to obtain maximal efficacy and minimal toxicity was initiated. By comparing the circulating drug concentration determined at a late and less variable stage of drug elimination to a population-representative database relating circulating drug concentration to therapeutic response, a rational approach to the optimization of dose for the individual patient was theoretically obtained (Figure 2).

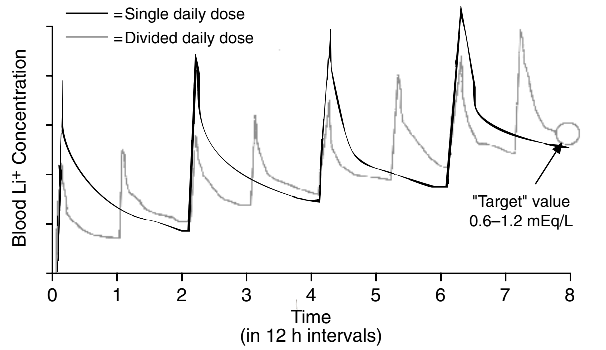
Drug concentration determinations are typically determined at steady state (after > 5 drug half-lives). This technique offered great promise in the control of interindividual pharmacokinetic differences in designing individualized treatment plans in psychiatry and has been shown by some estimates to be highly useful and cost effective.[5] However, for the great majority of drugs used in psychiatry, this potential has gone largely unrealized. Lithium represents a certain exception, in that the routine monitoring of serum lithium concentrations has expanded greatly the safety, tolerability, and efficacy associated with oral lithium dosing.

The most common problem associated with the routine application of therapeutic drug monitoring is the lack of well-established ranges or threshold values of circulating drug concentration associated with the highest probability of therapeutic benefit. In large part due to the unique, relatively simple pharmacokinetics of lithium, a range of serum lithium concentrations of 0.6 to 1.2 mEq/L is generally recognized as being associated with the safe and effective use of lithium. Serum lithium concentrations less than 0.6 mEq/L are associated with a significantly higher rate of relapse of symptoms of bipolar illness and with poorer psychosocial functioning.[25,26] Adverse events of lithium increase greatly when serum concentrations exceed 1.5 mEq/L,[7] while plasma lithium concentrations exceeding 3.5 mEq/L are often associated with life-threatening intoxication. It is unquestionable that the routine application of therapeutic drug monitoring to the use of lithium in psychiatry has greatly enhanced the safety of prescribing lithium salts to patients.

Divided Daily Doses or Single Nighttime Dose

Lithium salts are typically dosed as two or three divided daily doses to minimize the magnitude and negative consequences of postdose peaks and troughs in circulating lithium concentrations. While generally accepted as an effective means of enhancing the safe use of lithium salts in psychiatry, this practice places a larger burden on the drug-taking compliance of patients. The practice of administering lithium in divided daily doses is not universally accepted. The administration of a single daily nighttime dose of lithium salts has some support as an alternative strategy for lithium dosing. The availability of a daily recovery period for organ function, perhaps particularly renal, is thought to represent the major benefit of this strategy.

Figure 2. Principle of Therapeutic Drug Monitoring of Serum Lithium Concentrations*



*Serum concentrations following the oral administration of lithium carbonate are modeled for a single and divided daily dose. Trough lithium concentrations determined at steady state are compared against a therapeutic target range of values and, if necessary, doses are adjusted.

Slow-Release Lithium Preparations

The use of slow-release lithium formulations, often referred to as sustained- or controlled-release preparations, has been proposed as a means of diminishing the postdose variation in serum lithium concentration and the acute toxicosis associated with the C_{max} values observed after administration of immediate-release lithium preparations. Slow-release forms of lithium salts were developed for clinical use more than 30 years ago in Scandinavian countries. These early slow-release preparations utilized crude biopharmaceutical compositions. The slow-release preparations Quilonum Retard® and Lithium-Duriles® were introduced for clinical use in the Federal Republic of Germany in 1970. A total of eight slow-release lithium preparations were available in Europe by the mid 1970s. A marked geographical preference exists in the clinical use of slow-release lithium preparations. While popular in Europe for 2 decades, slow-release lithium preparations have only been available in the United States since the 1980s. Lithobid® and Eskalith CR® represent the major slow-release lithium preparations currently available in the United States.

Surprisingly few studies have examined the in vitro dissolution rates and in vivo pharmacokinetics of slow-

release, compared with immediate-release, lithium preparations. The in vitro rate of release of seven commercially available lithium preparations designated as slow- or sustained-release forms have recently been characterized.[27] The comparative rates of lithium release were assessed by serial sampling from stirred solutions of 0.1 M hydrochloric acid (pH $\simeq$ 1). The results obtained indicated marked differences in the release rates of slow- or sustained-release lithium for the different preparations as well as between batches for some slow-release preparations. Lithobid®, Eskalith CR®, Lithium-Duriles®, and Quilonum Retard® exhibited lithium release rates (i.e., $t_{1/2}$ ~ 60 min.) consistent with their designation as slow-release preparations. The results obtained did not support a slow-release rate for Lithiofor® and also demonstrated wide differences among release rates for different batches of this preparation.

The time course of the serum lithium concentrations obtained after the administration of single oral doses of slow-release lithium carbonate formulations to healthy volunteers demonstrated the potential advantages of such preparations over immediate-release forms of lithium salts.[7] The peak serum lithium concentrations attained after the administration of slow-release formulations occurred 2 to 6 hours after their administration and were approximately one half the magnitude of those of immediate-release products after the same amount of time had passed. The single dose studies support the contention that slow-release lithium preparations would be better tolerated due to the observed decrease in postdose C_{max}.

Thornhill[28] examined the 24-hour profiles of serum lithium concentrations observed in a small sample of patients after the administration of first immediate-release and then slow-release lithium carbonate preparations. Five male patients were entered into a crossover design comparison of immediate-release lithium carbonate tablets (500 mg t.i.d.) and a slow-release lithium carbonate preparation (900 mg b.i.d.). Blood lithium concentration monitoring was performed at 2.5 hour intervals for a 24-hour period on Study Day 7 after the administration of the immediate-release and Day 14 after the administration of the slow-release lithium formulations. The manufacturer and specific formulation for the slow-release lithium preparation examined in this study were not provided. The comparative serum lithium concentration profiles supported the suitability of the immediate-release preparation for attaining therapeutic lithium concentrations and indicated an unexpectedly wide variability of lithium absorption among patients after administration of the slow-release lithium preparation. This variable profile of lithium absorption from a slow-release formulation administered to nonfasted patients is in sharp contrast to the remarkably constant lithium absorption observed after the acute administration of a slow-release preparation to fasted patients.[29] The author attributed the wide variability in lithium absorption from slow-release preparations in the more recent study as being due to individual variability in gastric emptying time and intestinal transit. While these data do not support the advantages of slow-release lithium formulations over their immediate-release counterparts, the significance of these findings is weakened by a number of flaws or omissions in the experimental design. No clinical response or side effect measures were used, the specific slow-release lithium formulation studied was not identified, a nonrigorous schedule of venous sampling was used, a very small sample size (N = 5) was studied, and a fixed order of administration of the two lithium formulations was used. Furthermore, the author reported that several of the patients studied chewed the slow-release lithium formulation prior to swallowing it. These flaws render the outcome of this study as inconclusive and support the comparison of slow- and immediate-release lithium formulations by using more rigorous experimental design and methods.

The theoretical advantages of slow-release lithium preparations over their immediate-release counterparts in terms of reducing the diurnal fluctuations in serum lithium concentration and associated adverse events have not been empirically established. In fact, claims of reduced bioavailability of, increased GI-related side effects with, and decreased patient compliance with the slower releasing lithium preparations have been made. While largely unsupported by evidence, these claims have undoubtedly limited the clinical usage of slow-release lithium preparations in psychiatry.

SUMMARY

The use of lithium arguably represents the greatest contribution of inorganic chemistry to clinical medicine. The long record of documented efficacy of lithium salts in the treatment of debilitating mood disorders is offset by equally well-documented profiles of adverse events associated with its use. The oral administration of immediate-release preparations of lithium salts is associated with high postabsorptive serum lithium concentrations which are related to transient adverse events. Symptomatic manic states may be associated with the lithium serum concentration troughs that occur in late phases of lithium elimination. These sequelae of immediate-release oral lithium dosing support the nonideal nature of this route of lithium salt administration in routine psychiatric practice. Relative to other psychiatric medications, lithium exhibits unique pharmacokinetic properties, and its distribution in the human body is relatively unopposed by biological barriers. The relatively recent application of in vivo ^{7}Li MRS techniques to the study of brain lithium concentrations in the living human brain offers significant potential for an improved understanding of the pharmacokinetic basis of lithium response and nonresponse. The application of therapeutic drug monitoring to the use of oral lithium dosing remains the most successful means of balancing the

therapeutic efficacy and serious side effects associated with lithium administration. The theoretical advantages of slow-release lithium preparations over their immediate-release counterparts in minimizing postdose toxicosis and enhancing patient compliance remain largely unestablished. A significant need exists for head-to-head comparisons of the pharmacokinetics and clinical response relationships for major slow-release and immediate-release lithium formulations.

Drug name: sustained-release lithium (Eskalith, Lithobid).

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