LITHIUM: A CLINICAL UPDATE

Lithium's role in the treatment of patients with affective disease has revolutionized psychiatric practice over the past decade. During this time clinical research has been very effective in delineating those psychiatric disorders in which lithium is unquestionably the most efficacious treatment. More recently, it has been documented that some patients develop serious renal complications during lithium treatment. Thus, clinical criteria used in considering lithium maintenance will be discussed and emphasized along with methods to minimize nephrotoxicity. Much of the clinical research on lithium has developed data which is highly usable for the practicing clinician and contributed greatly to the art and the science of the clinical application of this important therapeutic tool.

Following are copies of the pertinent slides which will be used in the talk entitled "Lithium - A Clinical Update". These tables have been selected to address specific questions in regard to clinical use of lithium. One way in which these tables can be used is for the participants to fill in the details as they emerge from the talk by taking notes directly on the tables themselves.

Like many medications which have proven efficacy, lithium has evolved from being a drug which was under-utilized by practicing clinicians in syndromes for which it had established therapeutic efficacy to a compound which is often over-utilized in conditions for which there is no established efficacy. This is particularly important, given the fact that very recent data has emerged which indicate that the long term use of lithium is not as uncomplicated as it was previously thought to be.

The following table outlines the conditions for which lithium is unquestionably effective and those for which it is not.

PSYCHIATRIC CONDITIONS FOR WHICH LITHIUM HAS THERAPEUTIC EFFICACY OR POTENTIAL EFFICACY

THERAPEUTIC EFFICACY HAS BEEN ESTABLISHED:

- BIPOLAR DEPRESSION
  - TREATMENT OF ACUTE MANIA AND HYPOMANIA
  - PROPHYLAXIS OF MANIC AND DEPRESSIVE EPISODES

THERAPEUTIC EFFICACY APPEARS TO BE EMERGING, BUT IS NOT ESTABLISHED:

- PROPHYLAXIS OF UNIPOLAR DEPRESSION

PROMISING, BUT AWAITS MORE AND BETTER DOCUMENTATION:

- ALCOHOLISM - PARTICULARLY WITH ALCOHOLICS WITH AFFECTIVE DISEASE (DEPRESSION)
- AGGRESSIVE BEHAVIOR AND CHRONIC ASSAULTIVE BEHAVIOR
- ATYPICAL AFFECT DISORDER (SCHIZOAFFECTIVE?)

NO DOCUMENTATION OF THERAPEUTIC EFFICACY:

- GILLES DE LA TOURETTE SYNDROME
- PAIN SYNDROMES
- BORDERLINE STATES
- TARDIVE DYSKINESIA

The following two tables briefly outline the specifics of lithium's clinical use and will allude to certain of its pharmacokinetic properties. One slide details the method by Cooper et al. of predicting lithium dosage requirements in a specific patient by the use of a 600 mg single loading dose technique.

LITHIUM

THERAPEUTIC SERUM LEVELS 0.8 mEq/L to 1.6 mEq/L

DOSE: 600 mg to 3000 mg/day

DOSE SCHEDULE: TID, BID or QD H.S.

ONSET: THERAPEUTIC EFFECT 7 - 10 DAYS

HALF LIFE: 24 HOURS

DOSAGES REQUIRED TO ACHIEVE A SERUM LEVEL OF 0.6 - 1.2 mEq/liter

24-Hour Serum Level After Single Loading Dose	Dosage Required
Less than .05	1200 mg. three times a day
.05 - .09	900 mg. three times a day
.10 - .14	600 mg. three times a day
.15 - .19	300 mg. four times a day
.20 - .23	300 mg. three times a day
.24 - .30	300 mg. twice a day
More than .30	300 mg. twice a day**

Cooper et al, 1973

The following table outlines the more common side effects patients experience while on lithium. The range extends from the most mild and benign to those of a much more serious nature. There is an indication of those early signs and symptoms which indicate lithium toxicity.

COMMON LITHIUM SIDE EFFECTS

VERY MILD	NAUSEA (PARTICULARLY DURING FIRST FEW DAYS OF TREATMENT)
	FINE TREMOR OF HANDS
MILD TO MODERATE	ANOREXIA
	VOMITING
	DIARRHEA
	"UPSET STOMACH" OR "ABDOMINAL PAIN"
	THIRST AND/OR POLYURIA
	MUSCULAR WEAKNESS
	MUSCLE HYPERIRRITABILITY WITH TWITCHING, MUSCLE FASCICULATION, OR CHRONIC MOVEMENTS
	SEDATION, SLUGGISHNESS, LANGUIDNESS, DROWSINESS, GIDDINESS, COARSE TREMOR
	ATAXIA
MODERATE TO SEVERE	HYPERTONIC MUSCLES
	HYPERACTIVE DEEP TENDON REFLEXES
	HYPEREXTENSION OF ARMS AND LEGS WITH GRUNTS AND GASPING
	CHOREA, ATHETOTIC MOVEMENTS
	IMPAIRMENT OF CONSCIOUSNESS
	SOMNOLENCE, CONFUSION, STUPOR
	SEIZURES
	TRANSIENT FOCAL NEUROLOGICAL SIGNS
	DYSARTHRIA
	CRANIAL NERVE SIGNS
VERY SEVERE	COMA
	COMPLICATIONS OF COMA
	DEATH

There is increased understanding of how to implement responsible medical management of patients during lithium maintenance. The following table outlines some of the general principles which should be used during maintenance and also the most informative and pertinent laboratory studies to obtain during the time a patient is being maintained on lithium.

MEDICAL MONITORING DURING LITHIUM MAINTENANCE

1. See patient approximately q 4 mo.
2. Twice yearly:

   Serum lithium

   Urine concentration test

   Routine urinalysis

   Creatinine
3. Yearly:

   T_4

   Serum electrolytes

   24 hour urine volume

   $>$ 2 liters → urine concentration test

   $>$ 3 liters → creatinine clearance

   EKG

Of increasing importance are the indications that long term lithium maintenance is not as benign a treatment modality as was formerly believed. The following table outlines the more common and serious of the long term medical complications from lithium's use.

POTENTIAL MEDICAL COMPLICATIONS OF LONG TERM LITHIUM MAINTENANCE

THYROID (PBI↓, FREE THYROXINE)

- MILD HYPOTHYROIDISM (REVERSIBLE)
- NON TOXIC GOITER (REVERSIBLE)

CARDIAC (SUPPRESSION T WAVE - EKG)

- EFFECTS ON SINUS NODE
- REPORTS OF CARDIAC DEATH
  - MALES
  - >60 YEARS
  - >10 YEARS ON LITHIUM
  - FAMILY HISTORY OF CARDIAC DISEASE

RENAL

- NEPHROGENIC DIABETES INSIPIDUS
  - 7 - 10%
- RENAL INTERSTITIAL FIBROSIS - AZOTEMIA
  - 10 - 15 % (?)

Unquestionably, the histopathological changes in the kidneys of some patients on lithium is the most serious and frequent medical complication encountered. As such it obviously influences clinical practice and may begin to involve medical legal issues as well. The first table outlines several simple steps the physician should consider when medical complications, including renal, arise during lithium maintenance. The following table outlines, in more detail, those techniques which have been identified as reducing the possibility of patients developing renal complications during lithium maintenance. The last table summarizes those studies currently available in the literature reporting data on the effect of lithium maintenance on renal function.

FACTORS THAT REDUCE THE POTENTIAL NEPHROTOXICITY OF LITHIUM

1. Avoid lithium toxicity
   - Use lower doses
   - Good balanced diet
   - Electrolytes balanced
   - Liberal fluid intake
2. Avoid dehydration
   - Liberal fluid intake
   - Monitoring during dehydrating conditions
3. Avoid long term concurrent use of neuroleptics and lithium
4. Avoid peaks in lithium levels during the 24 hr. day
   - Always use divided doses
   - Give lithium with meals

THERAPEUTIC CONSIDERATIONS WHEN COMPLICATIONS ARISE DURING LITHIUM MAINTENANCE

1. Reduce lithium dosage
2. Reassess risk:benefit ratio for patient on an individualized basis
3. Consider discontinuation of lithium maintenance
4. If decision to continue is arrived at, do so with formalized informed consent

STUDIES OF EFFECT OF LITHIUM MAINTENANCE ON RENAL FUNCTION

	TOTAL	POLYURIA	↓GFR	↑CREATININE	+BIOPSY
Hestebech et al., 1977	N=14 (>5 years)	--	--	--	13 of 14
Brante, et al., 1978	N=24 (>2 years)	N=2 (>6L/24 hr)	N=1	N=1	2 of 2
Hansen, et al., 1978	N=110	N=18 (>3L/24 hr)	N=9	N=9	18*of 18
Vestergaard, et al., 1978	N=150	N=58	N=16	--	--
Rafaelsen, 1978	N=37 (>5 years)	N=28	--	N=9	9 of 28
Hullin, et al., 1979	N=30 (8-12 years)	N=6	N=0	N=5	--**
Kincaid-Smith, et al., 1979	N=16	--	--	--	5 of 16+
Coppen et al., 1979	mean 5.5 yrs vs. pre-lithium patients	--	--	--	no difference lithium vs. non-lithium

* Focal interstitial cortical fibrosis
** ↑ADH secretion; ↓renal tubule response to ADH
\+ no difference between pre-lithium and lithium affect disorder patients

LITHIUM MAINTENANCE

Some general factors which must be considered in deciding whether to prescribe lithium maintenance:

1) When effective lithium maintenance can be among the most dramatically effective treatments in psychiatry.
2) Limited term, carefully monitored treatment trials may be warranted in disorders in which the indication is questionable. The important point here is to have reliable outcome measures and to be there to discontinue the treatment if it doesn't work
   - target symptoms or clinical goals
3) The decision for or against lithium maintenance for bipolar patients should take into account frequency (1st episode, slow cycles, rapid cycles) severity of episodes and course of onset (insight) and likely consequences of an episode.
4) While generally not a difficult or dangerous treatment - lithium maintenance does have potential side effects - short and long term toxicities associated with it. Not to be undertaken lightly. Not everyone should receive lithium.

Diagnoses for which lithium maintenance may be indicated:

1) Bipolar manic-depression**

   Type I, IIA, IIB, cyclothymia

   Effective in approximately 80% of cases - problem of definition

   Major problem is compliance

   Adequate maintenance leads to rare manic episodes

   ** Efficacy shown in at least two controlled studies

Mild-moderate depressions are not infrequent

Antidepressants synergize with lithium

Rapid-cycles do worse but deserve a trial

After 3-5 years without episodes -? attempt discontinuation

2) Unipolar depression** Generally not the treatment of choice

Inquire about hypo-hypomania

Family history of bipolar disorder

Statistically about equal to tricyclic maintenance in efficacy

(but N's are small)

(well reviewed in JM Davis article)

3) Schizo affective disorder**

Not as effective as in typical bipolar illness

Probably worth a try first because of tardive dyskinesia

4) Alcoholism**

Two placebo controlled studies have found lithium helpful in depressed alcoholics (post-detox) but not in non-depressed

May change taste of Etoh or block highs

5) Episodic Aggression*

Sheard, Am. J. Psychiatry 133: 1412, 1976

6) Emotionally unstable character disorder* Important and frequent question

Rifkin et al, Arch. Gen. Psychiatry., 27: 519, 1972

** Efficacy shown in at least two controlled studies

* Efficacy in only one controlled study

Relative Contraindication (laboratory)

1) Renal (creatinine, urinalysis) think of Tegretal
2) Heart - (EKG if indicated) sinus arrhythmias, acute MI
3) Pregnancy
4) Electrolyte imbalance
5) Acute neurologic disorders
6) Thyroid (T4)

go more slowly
be more careful
monitor

Doses and blood level monitoring

1) Plasma levels are done 12 +/- 2 hours after last dose
2) Usual to begin 900-1200 mgm/day and monitor blood levels weekly x3, later q 1-3 months
3) Usual maintenance blood level 0.7-1.1 meq/L. Some patients do well as low as 0.4

Management of Recurrences

1) Educate patients and families to recognize symptoms <u>especially hypomania</u>
2) Mania/hypomania - increase lithium add antipsychotics <u>CLOSE FOLLOW-UP!</u>
3) Depression - <u>increase</u> lithium, add antidepressant

Side Effects and Toxicity - important to maintain conceptual distinction

<u>Side Effects</u>	<u>Toxicity</u>
Single	Multiple symptoms
Therapeutic Levels	Toxic levels
Normal EEG	Abnormal EEG
May not be dose related	Dose related

Side Effects

1) Neurologic - weakness, tremor (Propranolol 20-120 mgm during the day) or prior to fine motor work
2) Nausea, vomiting - change preparations - take with food
3) Weight gain - edema - treatment with spironolactone
4) Polyuria, nephogenic diabetes insipidis - treatment with thiazide diuretics
5) Dermatologic - acne, psoriasis
6) Leukocytosis
7) Thyroid

   Inhibition of TSH induced T_3 and T_4 release mild goiter with elevated normal T_4, rare clinical hypothyroidism

   All of the above are reversible when lithium is discontinued

Toxicity

1) Educate family and patient about early signs nausea, vomiting, diarrhea, ataxia, dysarthria
2) Renal toxicity

   Some portion of chronically maintained patients will develop decreased renal function and micropathology

   All patients should have creatine and urinalysis checked q 6 months. If these are abnormal and polyuria develops, do more sensitive tests (creatinine clearance, concentration test)

THERAPEUTIC DRUG MONITORING: LITHIUM

Lithium therapy is approved for treatment of acute manic episodes and prophylaxis of bipolar affective disorders. Lithium may have a beneficial effect on other disorders including acute depression, schizoaffective disorders and prophylaxis of unipolar depression. Lithium has a narrow therapeutic range and doses required to produce levels within this range vary widely from one individual to another. As such, an individualized approach to lithium dosing and monitoring is essential for safe and effective use. Monitioring and assessment of therapeutic response, side effects, serum lithium levels and provision of patient education are important components of monitoring lithium therapy.

MONITORING THERAPEUTIC RESPONSE

Goals for lithium therapy should be established for individual patients. The efficacy of lithium therapy is then based upon a comparison between initial goals for therapy and actual outcome of therapy. Therapeutic goals for the acutely manic patient should include control of specific "target" symptoms such as hyperactivity, flight of ideas, grandiosity, expansive mood, etc. Therapeutic goals for prophylaxis of recurrent affective disorders would be a decrease in the frequency of relapses (optimally no relapse occurs). A similar approach to monitoring therapeutic response should be utilized when lithium is prescribed for other medications.

Lithium therapy is effective in 60 to 80 percent of acutely manic or hypomanic patients. Response to lithium is usually evident in 6-10 days following initiation of therapy. Lithium is effective for decreasing relapses in both bipolar and unipolar affective disorders. Compared to placebo, lithium will decrease relapse rate by 25 to 50 percent.

LITHIUM SIDE EFFECTS

Adverse effects occur frequently during the initiation of lithium therapy. A fine tremor of the hand occurs in 50 to 60 percent of patients, thirst and mild polyuria in 60 percent, muscle weakness in 40 percent, gastrointestinal complaints including bloating, anorexia, nausea, vomiting, loose stools, diarrhea in 30 to 40 percent. Mild sedation or fatigue are frequent complaints. These side effects decline with continued therapy, although 25 percent of patients may continue to have thirst and polyuria and 4 percent tremor. Patients should be counseled to expect some unpleasant side effects, but that they are usually transient and benign. Common side effects encountered during lithium therapy are listed in Table 1. Side effects occur with increasing frequency at concentrations above 1.5 mEq/L, although severe neurotoxic effects have been reported to occur at therapeutic levels. Erythrocyte lithium levels may be better indicators of neurotoxic effects than serum concentrations. The elderly, schizophrenic patients and those with organic brain syndrome are reportedly at a

higher risk for neurotoxicity of lithium compared to other patients. Altered pharmacodynamics (drug concentration-effect relationship) or intracellular distribution of lithium are proposed as causes of increased risk of toxicity in these patients.

LITHIUM INTOXICATION

Except in cases of deliberate overdoses, lithium intoxication usually follows events resulting in sodium loss, dehydration or intercurrent illnesses decreasing the elimination of lithium. The syndrome of lithium toxicity (Table 2) develops over a period of four to five days as the patient continues to take his/her prescribed lithium dose in the face of decreased lithium clearance. The patient should be instructed to be aware of early signs of intoxication (Table 2) and to stop lithium if they become apparent. Although lithium levels are only a rough guide to the degree of toxicity, early signs are usually seen at lithium levels of 1.5 to 2.5 mEq/L. Serious toxicity occurs at concentrations above 2.5 mEq/L and life-threatening toxicity at concentrations greater than 3.5 mEq/L. For mild to moderate toxic symptoms, stopping the lithium therapy and allowing concentrations to drop to therapeutic levels is usually adequate therapy. In cases of severe toxicity with 12 hour lithium levels above 2.5 mEq/L, hemodialysis will rapidly clear lithium from the serum. Upon discontinuation of hemodialysis, a rebound of serum lithium concentration may occur as lithium reequilibrates from the peripheral tissues. Repeated

courses of hemodialysis may be necessary to decrease concentrations to non-toxic levels.

MONITORING LITHIUM LEVELS

Serum lithium levels are an indirect measurment of lithium concentration at sites of activity and toxicity, nonetheless, these levels are closely related to both therapeutic efficacy and side effects. Inadequate concentrations may result in treatment failure, depriving the patient of a potentially useful therapy, whereas high concentrations result in serious toxicity. Therefore, one of the primary goals of lithium therapy is maintaining the patient's serum lithium level within a narrow therapeutic range. Understanding how the body handles lithium will aid the clinician in obtaining and maintaining "therapeutic" lithium levels while minimizing side effects and toxicity.

LITHIUM LEVELS

Recommended lithium levels for the acute phase of treatment are 0.8 to 1.4 mEq/L. The therapeutic effects of lithium may not be apparent for 5 to 10 days following initiation of therapy and full effect may require a number of weeks. Lithium levels of 0.6 to 1.2 mEq are recommended for "maintenance phase" therapy following acute symptom improvement or prophylactic therapy. Lithium levels greater than 1.5 are associated with a high incidence of side effects and do not appear to provide additional therapeutic effects.

Obtaining blood samples for determination of lithium must be carefully controlled and standardized so as to allow comparison of levels within an individual patient over time, as well as comparison to those reported in the literature. The therapeutic range for lithium is based on "standardized 12 hour lithium levels". Blood for determination of lithium concentrations should be obtained 12 hours following the last daily dose. Morning doses must be held until the sample is obtained. Steady-state lithium concentrations will be attained three to seven days following the initiation of a dosage regimen. Levels determined prior to this time may be lower than those at steady-state. At steady-state, standardized lithium levels for a given dosing regimen should be reproducible to $\pm$ 0.10 mEq/L. Factors which may produce fluctuations in lithium levels for a given regimen include altered sampling time, patient noncompliance, assay variability, changes in sodium balance, drug interactions, changes in lithium preparation used and intercurrent illnesses altering lithium kinetics (see Tables 3 and 4).

Laboratory determination of lithium levels is most frequently performed utilizing either flame photometry or atomic absorption spectrometry. The instruments for both methods are widely available and used for a number of other clinical analyses. Both methods are adequate for routine monitoring of lithium therapy.

Measurement of saliva lithium concentrations has been proposed as an alternative to serum levels. Reported average saliva/serum lithium

ratios are 2.2 to 2.3, but range from 1.8 to 3.6 for different individuals. Establishing an individual's saliva/serum ratio may allow monitoring using saliva alone.

Determination of erythrocyte lithium concentrations and/or erythrocyte lithium/plasma lithium ratios has been proposed as a more accurate determinant of brain lithium levels. Preliminary data suggests that erythrocyte lithium levels may be better indication of both therapeutic response and toxicity than serum levels. The proposed therapeutic range for erythrocyte lithium concentrations is 0.2 to 0.6 mEq/L.

LITHIUM HANDLING

Lithium Preparations/Absorption

All commercially available products are all well absorbed, though the rate of lithium absorption is dependent upon the type of formulation prescribed. Available lithium formulations are listed in Table 5. Lithium citrate solution (8mEq Lithium/5 ml) and standard lithium carbonate capsules or tablets (8mEq Lithium/300 mg), are rapidly absorbed, producing peak serum levels between 0.5 and 2.0 hours following ingestion. The absorption rate of these products results in rapidly rising serum lithium concentrations and transiently high peak levels following each dose (Figure 1). A dose of 600 mg lithium carbonate (16mEq Lithium) as standard capsules may increase serum lithium levels 0.6 to 0.9 mEq/L above predose levels. The rapid increase of lithium levels and high peak concentations have clinical implications. First,

some acute gastrointestinal side effects (anorexia, nausea, vomiting, gastrointestinal distress, etc.) are associated with rapidly rising serum concentrations. These side effects can be minimized by administering doses on a full stomach or prescribing lithium in smaller, more frequent doses. Secondly, following each dose the kidney is exposed to high, possibly nephrotoxic concentrations. Preliminary data suggests that both the number of daily doses (and therefore peaks) and height of peak concentrations are important determinants of lithium induced distal nephron dysfunction.

Controlled release lithium carbonate preparations may minimize problems associated with rapid absorption and high peak concentrations. These products produce peak concentrations 0.2 to 0.4 mEq/L greater than predose levels at 3 to 6 hours following doses of 16 mEq (600 mg lithium carbonate). The lower, delayed peak levels allow less frequent dosing, may cause less gastrointestinal side effects and possibly result in lower incidence or severity of renal toxicity.

Lithium Elimination

Lithium is primarily excreted through the kidney, with negligible amounts lost through sweat and the GI tract. Because lithium is not bound to plasma protein, it is freely filtered at the glomerulus. In the proximal nephron, 70 to 80 percent of filtered lithium is reabsorbed through an active process. Lithium is not reabsorbed in the distal tubules or collecting ducts. Thus, lithium clearance is 20

to 30 percent of glomerular filtration rate (or creatinine clearance). The mechanism for the reabsorption of lithium in the proximal tubule is the same as that for the reabsorption of sodium, so that factors which influence proximal tubule sodium reabsorption will similarly influence lithium reabsorption. Lithium reabsorption will be increased (and therefore decrease excretion) by factors increasing proximal tubule sodium reabsorption such as thiazide diuretics, dehydration or sodium depletion. Because 98 to 99 percent of filtered water, but only 70 to 80 percent of filtered lithium is reabsorbed, distal nephron lithium concentrations may be up to 35 times the corresponding serum level. These high distal nephron lithium concentrations may be the important factor in determining nephrotoxicity of lithium.

In patients with normal renal function elimination, the half-life of lithium is usually 18 to 36 hours.

A number of factors influence lithium elimination rate (Tables 3 and 4). Most, but not all of these factors may be explained by their effects on renal lithium excretion. Longer half-lives have been reported in patients receiving lithium for one to two years compared to those initiating therapy. Similarly, bipolar patients have been reported to have longer half-lives compared to unipolar patients. These longer half-lives may be due to alterations in the intracellular distribution of lithium, with a longer half as a secondary effect.

DOSING

Because of the narrow therapeutic range and interpatient variability in pharmacokinetics and drug tolerance, lithium dosage should be determined on an individual basis. Initial daily lithium carbonate doses of 1200 to 2400 mg given in two to four doses should be utilized for treating acute episodes. During the acute episodes, some patients may require up to 3000 mg/day of lithium carbonate to maintain therapeutic concentrations. Elderly patients, patients with reanl impairment, decreased cardiac output or other factors which decrease elimination of lithium may require smaller doses and closer serum level monitoring to avoid toxicity. Such patients should be prescribed lower initial doses, with dosage adjustment based on lithium level determinations. Lithium levels should be determined one to three times during the first week of therapy with appropriate dosage adjustment to attain lithium levels of 0.8 to 1.4 mEq/L. Changes in lithium doses will produce proportional changes in steady-state concentrations. For example, if a patient receiving 1200 mg of lithium carbonate per day has a steady-state lithium level of 0.6 mEq/L, doubling the dose to 2400 mg/day should produce a steady-state concentration of 1.2 mEq/L. Patients failing to show response to lithium therapy in 6-10 days should have their lithium doses increased to obtain maximum therapeutic serum levels (1.3 to 1.4 mEq/L). Following control of symptoms, "maintenance" lithium doses which produce lithium levels of 0.6 to 1.2 mEq/L are recommended.

When initiating lithium therapy for prophylaxis of recurrent affective disorder, start with low doses (i.e. 300 mg lithium carbonate b.i.d.) and slowly increase to doses which produce lithium levels of 0.6 to 1.2 mEq/L. By slowly increasing the dose many of the initial side effects encountered with lithium therapy can be avoided or minimized (see side effects).

Due to the wide variability of lithium dosage requirements and the difficulty in predicting individual dosage needs, a number of methods have been proposed to rapidly determine lithium doses. These methods utilize a single or a series of lithium levels to determine an individual's lithium dosage needs. All methods have limitations due either to complexity of the protocol or limited efficacy in non-research settings. The practicality and accuracy of any dosing method should be verified in the clinical setting in which it is to be utilized.

DRUG INTERACTIONS

Lithium interacts with a number of frequently used therapeutic agents. Two types of interactions occur: 1) those which alter lithium levels, and 2) those which result in toxicity without concurrent increases in lithium levels (Table 3). Most drugs which alter lithium levels do so through changes in renal handling of lithium. Drugs such as thiazide diuretics decrease lithium clearance by increasing proximal tubular reabsorption. Xanthine agents such as caffeine or theophylline increase lithium clearance by increasing renal blood flow and glomerular filtration rate. Drugs which alter lithium clearance are listed

in Table 4.

The concurrent use of lithium and certain other agents have been reported to result in an increased risk of toxicity. Combined use of lithium and antipsychotic agents, in particular haloperidol, has been reported to result in severe neurotoxicity at therapeutic lithium concentrations, however, antipsychotic drugs are frequently used concurrently with lithium, and the risk of neurotoxicity from the combination is low.

The incidence of toxicity resulting from concurrent use of the other drugs listed in Table 4 is rare in relation to the number of patients in which the combination has been prescribed and found to be safe.

INITIATING LITHIUM THERAPY

A careful workup is required for all patients initiating lithium therapy. The extent of such a workup should be individualized, based upon each patient's past medical history. The essential features of such a workup are listed below.

1. Establishment of goals for lithium therapy. Monitoring the therapeutic efficacy of lithium should be based on a comparison of the initial indications for therapy and actual outcome of therapy (i.e. for acute manic episode: decreased activity, flight of ideas, grandiosity, pressured speech, etc. For prophylactic therapy: maintenance of euthymic state.)

2. Assessment of organ systems affected by lithium (Table1).

   a. Kidney

      Baseline assessment of the kidney function should include a serum creatinine determination, a urinalysis and estimate of 24 hour urine output. For patients with pre-existing renal disease, a measured 24 hour creatinine clearance and estimate of urine concentrating ability may be desired.

   b. Thyroid Function

      Baseline T_3, T_4, and TSH should be determined. The thyroid should be palpated to determine the presence or absence of goiter.

   c. Cardiovascular System

      Baseline EEG should be obtained in elderly patients or those with preexisting cardiovascular disease.

   d. Hematologic

      A baseline CBC should be obtained to monitor changes in blood counts, particularly leukocytosis.

   e. Weight

      Significant weight gain may be a side effect of lithium.

3. Assessment of organ systems and factors which influence handling of lithium (see Tables 3 and 4).

   a. Renal - determination of serum creatine.

   b. Cardiovascular - assess for evidence of decreased cardiac output.

c. Diet - Determine dietary sodium intake levels.

d. Presence of concurrent drug therapy which will alter lithium pharmacokinetics.

e. Electrolytes should be determined in those patients in which a question of electrolyte imbalance is present.

4. Existence of conditions or factors which are reported to increase the risk of lithium toxicity.

a. Elderly patients

b. Schizophrenia

c. Organic brain syndrome

d. Concurrent drug therapy (see Table 4)

e. Renal impairment

f. Cardiovascular disease

g. Sodium depletion or dehydration

There are no absolute contraindications to lithium therapy. Patients who have relative contraindications as listed above should be monitored closely for toxicity and effectiveness of lithium documented.

5. Incidence of preexisting symptoms which may otherwise be attributed to lithium.

a. Hand tremor

b. Gastrointestinal complaints

c. Thirst

d. Urinary tract problems

e. Neurologic status

6. Provision of patient instruction and education.
   a. Importance of compliance to prescribed regimen.
   b. Frequent but transient nature of mild, initial side effects.
   c. Importance of dietary changes, particulary sodium intake, avoid dehydration
   d. Addition or elimination of concurrent medications.
   e. Signs and/or symptoms of toxicity.
   f. Importance of blood level monitoring.

MONITORING LITHIUM THERAPY

Once lithium therapy is initiated, a plan for ongoing monitoring of the patient is imperative. Close monitoring is required during the first few weeks of lithium therapy in order to establish the correct dose and to monitor for side effects. The essential components for ongoing monitoring of lithium therapy are listed below.

1. Monitoring of therapeutic response should be based upon the initial target symptoms for which lithium was administered.
2. Measurement of lithium levels and appropriate dosage adjustment as necessary.
   a. During the initial phase of treatment lithium levels should be drawn one to three times per week. Once patients are established on a dose resulting in the desired therapeutic levels and symptoms are controlled, monitoring levels every 4-6 weeks is usually adequate. Patients who have fluctuations in lithium

levels should be monitored more closely and questioned about compliance to the prescribed regimen. Less frequent levels may be obtained in patients in remission with stable lithium levels. Serum concentrations should be monitored following addition or deletion of other medications, changes in diet, intercurrent illness which may alter lithium levels and appearance of any symptoms consistent with lithium toxicity.

3. Monitoring of side effects should include the laboratory tests listed below as well as questioning the patients about the presence of side effects frequently encountered during lithium therapy (Table 1).
4. Laboratory monitoring for side effects (see Table 1).
   a. Because of the possible nephrotoxicity of lithium, serum creatinine should be determined every four to six months during the first year and then yearly following the first year of therapy.
   b. A urinalysis should be obtained every two to three months for the first year and then yearly unless polyuria or pre-existing renal impairment is present.
   c. If significant polyuria persists following the initial phase of the treatment or develops during therapy, a water deprivation/vasopressin test should be performed. [8] This test will determine the amount of urine concentrating defect present.

d. Measurement of TSH, T_3 and T_4 should be performed every four to six months for the first year and then yearly.

e. An electrocardiogram should be obtanied if there is any evidence of cardiovascular problems.

CONCLUSIONS

This article presents guidelines for the management and monitoring of lithium therapy. Therapeutic drug monitoring of lithium involves serum concentration measurements, side effect monitoring through use of patient interviews and laboratory tests, and determination of effectiveness. Safe and effective lithium therapy requires both a basic knowledge of lithium pharmacology and the use of individualized monitoring plans.

TL-MS9.5

TABLE 1 . SIDE EFFECTS OF LITHIUM THERAPY

Organ System	Comment
Neurologic	
tremor	Usually transient, if persistent (4%), treat with propranolol.
muscular weakness	Transient, mild
cogwheel rigidity	Transient, mild
increase slow wave EEG activity	Benign
decrease attention, concentration	Mild
lightheadedness	
seizures	
Gastrointestinal	
nausea, vomiting, anorexia diarrhea, loose stools, abdominal pain, bloating	Usually transient, associated with rapid rise in Li levels. Give with food, smaller more frequent doses or slow release products.
Renal	
nephrogenic diabetes insipidus, polyuria/polydisia	Usually mild, transient. Persistent in 25%, may be severe.
nephrotoxic	Importance of morphologic changes unclear. Incidence of nephrotoxicity is low in absence of toxic levels.
Cardiovascular	
T wave depression inversion	Benign
Increase PVC/arrhythmias	Rare
Sinus node dysfunction	Rare
Myocarditis	Rare
Thyroid	
hypothyroidism	Treat with thyroid supplement, occurs in 3.2% of patients.
euthyroid goiter	Occurs in 3.1% of patients.
increased TSH	Occurs in 10 to 20% of patients.
Hematologic	
leukocytosis	WBC increase 30-45%.
Dermatologic	
acne/acneiform	
exacerbation of psoriasis	
hair loss	
rash	
Miscellaneous	
metallic taste	
hyperparathyroidism (mild)	
weight gain	

TABLE 2. LITHIUM INTOXICATION

Early, mild to moderate symptoms (Li levels 1.5 - 2.5 mEq/L)

- Course tremor
- Ataxia
- Sedation/sluggishness/confusion
- Giddiness
- Nausea/vomiting/gastrointestinal distress
- Diarrhea
- Lightheadedness

Moderate to severe symptoms (Li levels 2.5 - 3.5 mEq/L)

- Tinnitus
- Hyperreflexia
- Worsening tremor
- Dysarthria
- Hypertonic muscles
- Seizures
- Choreoathetosis
- Impaired consciousness
- Blurred vision
- Restlessness
- Profound weakness
- Nystagmus

Severe intoxication, Life-threatening intoxication
(Li levels usually > 3.5 mEq/L)

- Stupor/coma
- Hypotension
- Oliguric renal failure
- Death

TABLE 3. FACTORS ALTERING LITHIUM ELIMINATION

Decrease Elimination	Increase Elimination
renal impairment	acute phase of therapy
decreased cardiac output	increased sodium intake
elderly patients	concurrent drug therapy#
decreased sodium intake	
increased extrarenal sodium loss	
dehydration	
length of therapy*	
bipolar effective disorder*	
concurrent drug therapy#	

* preliminary data

see Table 3

TABLE 4. LITHIUM-DRUG INTERACTIONS

Drugs Altering Lithium Elimination

Decrease	Increase
Distal Tubule Diuretics thiazides metolazone chlorthalidone	Xanthine Drugs caffeine theophylline/aminophylline
Spironolactone	Acetazolamide
Non-steroidal Antiinflammatory Agents indomethacin phenylbutazone ibuprofen probably others	Furosemide#
Methyldopa*	Chlorpromazine
Tetracycline*	Osmotic Diuretics
	Sodium Dicarbonate

* Rare case reports only
\# Case reports of furosemide related lithium intoxication, though controlled studies demonstrate no change or increased elimination

Drugs Associated With Increased Toxicity (without toxic Li levels)

	Comment
Antipsychotics haloperidol fluphenazine chlorpromazine thioridazine	Case reports of severe neurotoxicity, particularly with haloperidol. Compatible in most cases.
Neuromuscular Blocking Agents	Prolong duration of N-M blockade
Digoxin	Potentiate digoxin toxicity?
Baclofen	Hyperkinetic movements?
Methyldopa	Case reports of neurotoxicity
Phenytoin	Case reports of neurotoxicity

TABLE 5. AVAILABLE LITHIUM PRODUCTS

Lithium Carbonate (8 mEq lithium per 300 mg)

Capsules 300 mg - Eskalith
Lithonate
other various manufacturers

Tablets 300 mg - Lithotabs and others

Controlled release products

- Lithobid 300 mg tablets
- Eskalith CR 450 mg tablets

Lithium Citrate (8 mEq / 5 ml)

- Cibalith S and others