Chapter II

The literatures review

Review of lithium

Natural spring waters containing lithium were reputedly used by the Greeks as treatment of "ill humour" and "excitement". The first published clinical study of lithium salts in the treatment of mania was that of Cade in 1949. In 1954 , Schou and associates confirmed the antimanic effect of lithium (Peet and Pratt,1993).

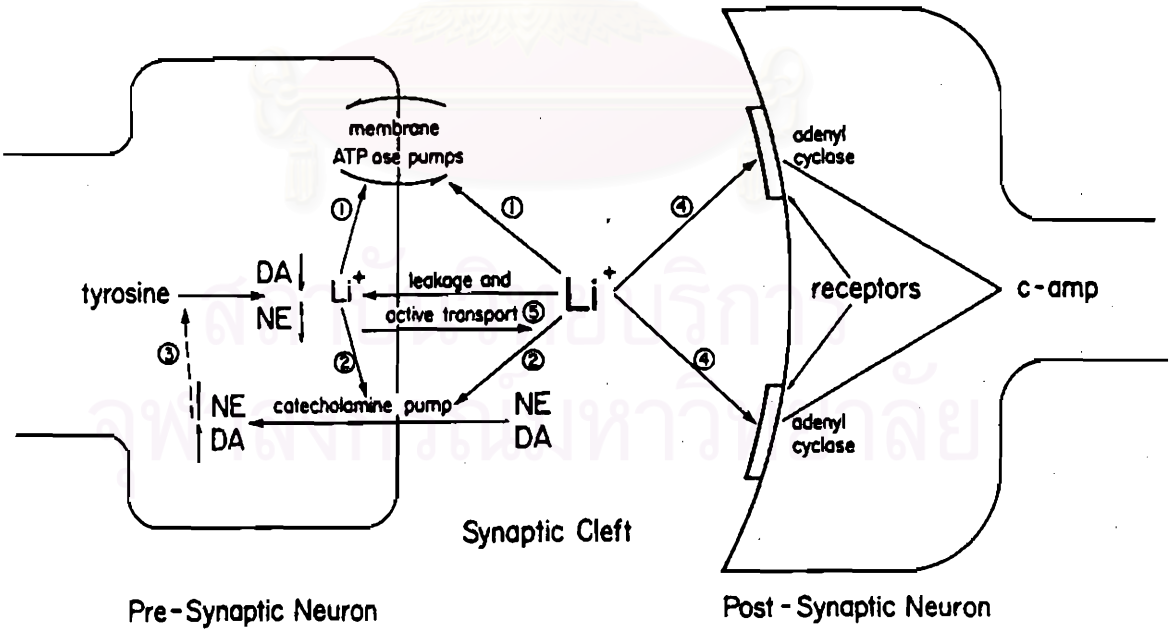
Lithium is a monovalent cation that is used primarily in the therapy of bipolar disorders (acute manic episode and prophylaxis against recurrence). Other uses of lithium include adjunctive therapy for depression, schizophrenia, aggression, syndrome of inappropriate natridiuretic hormone (SIADH), cluster headache, and as immunologic adjuvant (Vertrees and Ereshefsky, 1995). Although lithium has been used in a variety of psychiatric and medical illness, its FDA approved indications include the acute treatment of mania and maintenance treatment of bipolar disorder (Physician Desk Reference, 1990). The choice between lithium and other effective interventions in each indications is a matter of clinical judgement.

A. Pharmacological properties

Many hypotheses have been proposed to explain the mechanisms for lithium's pharmacological effects. These range from relatively simple theories of partial substitution for various cations (Na+, K+

, Mg++ , Ca++) to more complex hypotheses involving inhibition of intracellular messengers. Current theories center around lithium's ability to modulate the second-messenger system of cAMP, cGMP, and phosphatidylinositol, as well as its ability to increase the turnover rate of neurotransmitter, for example ,norepinephrine and serotonin (Vertrees and Ereshefsky, 1995). The many diverse effects of lithium make it unlikely that any one mechanism is responsible for its therapeutic effects.

FIGURE I. LITHIUM'S MECHANISM OF ACTION.



Depicts postulated mechanisms for lithium's action in mania. Li^+ can partially substitute for Na^+ and K^+ in several membrane pump systems (1), leading to alterations in the cellular electro-chemical microenvironment (2) that cause increased reuptake of dopamine (DA) and norepinephrine (NE). The intracellular DA and NE (3), by feedback inhibition, decrease catecholamine production and release. Alternately, lithium may decrease the sensitivity (4) of catecholamine or hormonal-sensitive adenyl cyclase receptors. The concentration of lithium inside the cell (5) is a result of active transport and "leakage" through the membrane.

B. Clinical pharmacokinetics

Absorption

Lithium is given orally. Lithium carbonate is the most commonly used salt form because it contains more lithium by weight than other salts (e.g.citrate,sulfate,glutamate,gluconate, and aspartate). Additionally carbonate products have a longer shelf-life. The effect of the different salts are similar since the therapeutic and adverse effects fundamentally depend on the lithium ion itself. After oral administration, lithium is nearly completely absorbed whether given as the carbonate or citrate salt (Amdisen and Carson, 1986).

Lithium absorption occurs primarily in the jejunum and ileum with negligible absorption in the colon (Carson, 1992). The rate of absorption of lithium depends on the dosage form (Ereshefsky and Jann, 1983). In normal fasting individuals , a solution of lithium (lithium chloride, 24 micromol) had an absorption half-life of approximately 0.15 hours with peak plasma concentrations 1 to 2.5 mmol/L occurring form is to 40 minutes after administration (Amdisen, 1977).

After oral administration of lithium carbonate capsules and tablets, time to peak plasma concentration is slightly longer than aqueous solutions and is usually form (not available in Thailand) usually peak between 2 to 6 hours,with peak plasma concentrations reaching 50 % of rapid release products (Amdisen and Carson, 1986). Lithium's bioavailability from standard-release tablets and capsules range from 80 to 100 % (Amdisen, 1977).

Administration of lithium with meal can delay its absorption significantly. Moreover, adverse effects of lithium (e.g. tremor, polyuria, weakness, nausea and vomiting) are related to both the rate of rise in the lithium serum and absolute maximum concentration achieved. Giving lithium with meals or as a controlled-release product can decreases the rate of absorption and the maximum peak concentration, and can help control these adverse effects (Vertrees and Ereshefsky, 1995).

Distribution

Lithium is distributed unevenly into different body compartments with an apparent volume of distribution (Vd) of 0.7-1.0 L/kg (Ward , Musa and Bailey, 1994). It is not protein bound nor metabolized. Tissues in which lithium is found include brain, muscle, bone, and kidney.

Lithium concentrations in plasma are twice that found in RBCs and CSF and similar to that found in umbilical cord , blood , cardiac and lung tissue. Higher concentration than plasma are found in saliva, brain, thyroid gland and bone (Ward et al., 1994). Uneven distribution of lithium into the brain might explain the rare cases of cerebral intoxication which may have been observed in patients with a serum lithium concentration below the range usually associated with toxicity (Carson,1992).

Lithium disposition is classically described using the open, two-compartment model. The central compartment volume has been found to be 25% to 40 % of the bodyweight and the combined central and peripheral compartments are equivalent to a mean of 123 % of the body weight (Carson, 1992).

Lithium is distributed slowly and proportionally to both the brain and erythrocytes. So a high or low erythrocyte (RBC) lithium concentration has been suggested as a measure of toxicity or noncompliance, even if plasma lithium levels are within the usual therapeutic range. However, the clinical use of this test may be limited because of the pronounced interindividual variablity of erythrocyte lithium concentrations (Carson, 1992).

Elimination

Lithium is eliminated renally as the free ion and is not bound by plasma proteins nor metabolized. It is considered to be freely diffusible across the glomerular membrane like sodium and potassium and is 80 % reabsorbed in the proximal renal tubules not in the distal tubules except in connection with an extremely low sodium intake (Carson, 1992). Elimination through saliva , sweat and feces is negligible. The initial distribution half-life averages 5 hours with a terminal beta half-life 18 to 36 hours both adults and children (Ward et al., 1994).

Elimination of lithium correlates with renal function. Normal lithium clearance in humans varies from about 10 to 40 mL/min. In patients with a normal sodium balance, lithium clearance is approximately 25 % of creatinine clearance (Winter, Koda-Kimble and Young, 1992).

Lithium Clearance = (0.25)(creatinine clearance)

Lithium clearance has been reported to change with posture ,e.g., clearance is increased when subjects are supine and decreased when subjects are standing (Ward et al., 1994). These facts with

consideration of convenience are the reasons to obtain blood samples for monitoring serum lithium concentration in the morning 12 hours following the previous evening's dose (Carson, 1992).

Although a number of drugs and diseases states can influence lithium clearance, the most important influences on clearance are renal function and sodium balance (Winter et al., 1992).

The disposition of lithium varies between subjects, but is relatively stable within any given individual with consistent renal function. This necessitates individualization of dosage regimens and monitoring adverse effects. The within-subject stability of lithium disposition allows estimation of chronic dosage requirements using population and pharmacokinetic prediction techniques.

Factors reported to affect lithium disposition and serum lithium concentrations showed in table I (Carson, 1992).

Table I Factors Reported to Affect Serum Lithium Concentration.

Alteration	Factors
Lower	Acetazolamide, aminophylline, caffeine, osmotic diuretics, pregnancy (a), sodium supplement
Variable or no effect	Amilioride, aspirin, furosemide, sulindac
Raise	ACE inhibitors, ibuprofen, indomethacin, chronic lithium, phenylbutazone, thiazides diuretics, dehydration, renal impairment, sodium loss, increasing age

(a) Lithium clearance and serum concentration return to pre-pregnancy values after delivery.

The interaction of lithium with other drugs can cause alteration in any phase of pharmacokinetic scheme. The list of commonly used drugs that interfere or change the usual pharmacokinetics and clinically significant drug interactions with lithium were summarized in table II.

Table II Potentially Clinically Significant Drug Interactions with Lithium.

Class / Generic name	Effect to Lithium Level	Recommendation
Antipsychotics		Observe the patient closely to detect neurotoxicity and worsening of EPS especially with high potency antipsychotics.
chlorpromazine	decrease	
fluphenazine	unknown	
haloperidol	unknown	
thioridazine	unknown	
Cardiac drugs		Avoid this combination where possible or monitor the patients carefully if not possible because of lithium may potentiate cardiac conduction effects.
digoxin	unknown	
methyldopa	possible increase	

continued.....

Class / Generic name	Effect to Lithium Level	Recommendation
Diuretics		Monitor blood lithium level carefully.
carbonic anhydrase inhibitors	decrease	
loop diuretics	unclear	
thiazides	increase up to 50 %	
osmotic diuretics	unclear	
potassium-sparing diuretics	increase	
xanthine derivatives	decrease	
Nonsteroidal anti-inflammatory drugs		Monitor blood lithium level frequently and aware intoxication.
diclofenac	increase	
ibuprofen	possible increase	
indomethacin	increase by 30-50 %	
naproxen	unknown	
piroxicam	increase	
phenylbutazone	unknown	
sulindac	less problematic than others	
Miscellaneous drugs		
sodium bicarbonate	decrease	Monitor blood lithium level carefully

Data from Lenox and Manji, 1995 ; Peet and Pratt, 1993 ; Salem, 1982 ; Sarid-segal, 1995.

Lithium and antipsychotics interaction

The practice of combination antipsychotics with lithium generally safe and efficacious but caution is recommended, particularly with the high-potency antipsychotics, haloperidol. There are several reports indicated that this drug interaction is pharmacokinetic interaction between antipsychotics and lithium, but they are not clinically significant. This interaction cause neurotoxicity. The syndrome is characterized by altered mental status, cerebellar signs and symptoms. It seems prudent for physicians to be more aware of this interaction and to discontinue both drugs if toxicity develops.

Lithium and antidepressants interaction

The combination of lithium and various classes of antidepressants has been used extensively in large number of patients. There are several reports of increased incidence of myoclonic jerk in patients receiving a combination of lithium and MAOIs, but more investigations are wanted.

Lithium and electroconvulsive therapy (ECT) interaction

In recent years, ECT has been remarkably efficacious, potentially life-saving treatment for a number of psychiatric conditions for which lithium is also used, including severe depression and mania. There have been several case reports suggesting that the lithium-ECT combination may be associated

with a neurotoxic syndrome characterized by confusion, disorientation, and decreased responsiveness. So it seems prudent to discontinue lithium during the course of ECT or use low therapeutic lithium levels and monitor for any symptoms suggestive of neurotoxicity (Lenox and Manji, 1995).

C. Dose of lithium

Dosing for Acute Therapy

Approved recommendations for initial therapy in adults suggest beginning with 300 to 600 mg of lithium carbonate tablets or capsules, three times a day ,or, for sustained-release products, initially 600 to 900 mg a day in three divided doses (USP DI, 1994). Thereafter the dosage should be individually adjusted according to serum concentrations and clinical response (target symptom response). Doses at the upper end of these recommendations may be associated with the limiting side effects (particularly gastrointestinal effects) , which may influence patients' long-term willingness to take lithium. Therefore , beginning with a dose of 300 mg of lithium carbonate (tablets) , two or three times a day for several days, before initiating the full desired starting dose, may minimize initial adverse effects and lead to increased tolerance of lithium therapy (Vertrees and Ereshefsky, 1995). Administration of two or more daily dose is recommended. A single daily dose should not be used , principally because the high peak concentration of this schedule should avoided when a near-toxic dosage is needed. Existing knowledge about the correlation between

control values and response concerns only those patients who have taken 2 or more doses per day , and furthermore, the high peak concentration of a single dose per day involves a higher risk of side effects (Amdisen, 1975). Dosage should adjusted with serum concentrations on a biweekly or weekly basis until a serum concentration of 0.8 to 1.2 mEq/L is obtained (Ereshefsky and Jann, 1983). Patients may occasionally require up to 80 mmol or mEq (3000 mg lithium carbonate) per day during the acute episode (Ereshefsky, Gilderman and Jewett, 1979a ; Ereshefsky and Jann, 1983).

Some patients who need only a low end of therapeutic range for therapeutic effect may also have a low lithium clearance, they therefore require very low dosages. Others who need a higher serum lithium concentration may also have high lithium clearances , these patients need very high daily dosages (Winter et al., 1992). Elderly patients or those with cardiovascular or renal impairment require close monitoring and cautious use of the drug, because the possibility of toxicity (Ereshefsky et al., 1979a).

Since response to lithium therapy has a lag period of seven to ten days, some patients require adjunctive neuroleptic therapy (phenothiazine, butyrophenone, thioxanthine, etc). When response to lithium has occurred and symptom control is evident, the dosage of the neuroleptic agent is gradually reduced (Ereshefsky et al., 1979a ; Peet and Pratt, 1993). Subsequently, the lithium dosage is gradually adjusted downward to a suitable maintenance level.

Dosing for Maintenance Therapy

The maintenance dose of lithium carbonate is usually ranging from 600 to 1500 mg per day (Ereshefskyet al., 1979a). Corresponding serum lithium levels are in the range of 0.5 mEq/L to 1.2 mEq/L. It has been suggested that measurement of the renal clearance of lithium before starting maintenance treatment can be used as a basis to calculate the maintenance dose. It has also been suggested that the maintenance dose can be determined on the basis of the 24-hour serum concentration after a given test dose (Cooper and Simpson, 1973). And this seems practicable in most cases (Cooper and Simpson, 1976). However, it is inadvisable to rely too implicitly upon such a once-only test. So many variables influence such a standardized serum concentration that the risk of calculating a wrong 24-hour dose is too great to be acceptable.

Without doubt, the safest way to establish maintenance dosage is to base the adjustment of the dose upon reported monitoring of the standardized 12-hour lithium concentration (12h-stSLi) during the period of adjustment. When 12h-stSLi is used as a guide during the continued course of treatment, its reproducibility, assuming unchanged renal elimination and distribution volume, is of major importance. Therefore, it is essential to attain accurate control of the various, importance variables such as compliance with medication intake, the dosage schedule, and the accurate interval of 12 hours between the evening dose and the blood sampling the next morning (Amdisen, 1983).

Predictive Dosing Method

As plasma concentration determinations are essential owing to lithium's therapeutic index, empirical dosing (i.e., dosing by patient response alone) is not recommended for routine clinical use. There are several methods available for prediction of lithium dosage and many are based on pharmacokinetic principle (Yukawa et al, 1993). Prediction accuracy ranges from 60 to more than 90 % , resulting in some patients who are underdosed and some patients who receive potentially toxic doses (Ward et al., 1994). The goal of dosing methods is to achieve a therapeutic lithium concentration with the first dosage regimen, thereby decreasing the time to response and at the same time avoiding toxicity. Requirement for such a method would be accuracy, particularly considering lithium's narrow therapeutic index, wide applicability across patients groups, and simplicity couples with a reasonable cost. Approximate dosing requirement is showed below.

$$D = \frac{Vd\ Ke\ \tau\ Cpssave}{F} \quad \text{or} \quad D = \frac{Vd\ (0.693/t_{1/2})\ \tau\ Cpssave}{F}$$

where D is dosage ; Vd is volume of distribution ; Ke is elimination rate constant ; τ is dosing interval ; Cpssave is average desired steady state serum concentration ; and F is Fraction absorbed. All the variables in the formula are known or can be calculated. The desired steady-state serum lithium concentration and the volume of distribution ranges (0.5 - 1.2 L/kg) are known. The elimination rate constant can be calculated

on the basis of renal clearance . The dosing interval is usually assumed to be 24 hours, and the fraction absorbed is assumed to be approximately 90 %. This formula can be applied to most patients (Vertrees and Ereshefsky,1995).

When using dose-prediction methods, clinical judgement in treating the patient should not be minimized. Because routine monitoring is still necessary, including obtaining lithium plasma concentrations, and because some methods require more than one blood sample or require urine collections, the use of dose-prediction methods is limited. The most widely used and perhaps easiest method is by given test dose 600 mg of lithium carbonate and a serum lithium concentration is determined 24 hours later. A nomogram is then used to select the dosage required to achieve a serum concentration between 0.6 to 1.2 mEq/L (Cooper et al, 1973). A simple equation also can be used instead of the nomogram :

$$Li^+ \text{ (mEq/day)} = e^{(4.80-7.5C_{test})}$$

Here C test is the lithium plasma concentration 24 hours after 600 mg of lithium carbonate (Vertrees and Ereshefsky, 1995).

D. Adverse drug reactions

Lithium has a narrow therapeutic index in humans, with a currently recommended therapeutic serum concentration range of 0.5 - 1.2 mEq/L (Ward et al., 1994). Side effects and toxicity become increasingly more evident at doses achieving higher serum levels. A recent review of the literature reveals that 35 -93 % of patients complain about adverse side effects of lithium treatment (Lenox and Manji, 1995). Side effects are

common during the phase of lithium treatment. Most of the side effects, however , are transient, and cause few problems for the patient. Patient counseling by pharmacists to explain the transient nature of these effects should increase compliance. The most common side effects reported and the initial side effects are noted in Table III (Goodwin and Jamison, 1990) and Table IV (Ereshefsky , Gilderman and Jewett, 1979b) respectively.

Table III Lithium side effects

Side effects	Percentage with subjective complaint (a)	Relative importance in noncompliance (b)
Excessive thirst	35.9	
Polyuria	30.4	4
Memory problems	28.2	1
Tremor	26.6	3 (c)
Weight gain	18.9	2
Drowsiness/tiredness	12.4	5
Diarrhea	8.7	
Any complaint	73.8	
No complaint	26.2	

a Pooled percentages from 12 studies including 1,094 patients.

b Relative ranking of importance of side effects for lithium compliance in 71 patients (Goodwin and Jamison,1990).

c Include incoordination.

Table IV Initial Side Effects of Lithium.

* Fine hand tremor	Muscle weakness
Anorexia	* Fatigue
Mild nausea	Drowsiness
Epigastric pain	* Thirst
* Loose stool	* Mild polyuria

* indicate side effects that may persist.

The major physiological systems predisposed to lithium-induced symptomatology and toxicity include the gastrointestinal, renal, endocrine, and nervous systems as well as the teratogenicity associated with the developing fetus. Most of the side effects appear to be dose related and transient in nature (Jefferson, 1990; Schou, 1989). Although sustained-release formulations of lithium may be useful in ameliorating some lithium-induced side effects, enhanced gastrointestinal symptomatology may preclude this treatment strategy. Thus, risk factors that predispose to side effects and toxicity of lithium include reduced renal clearance with age or renal disease, organic brain disorder, physical illness with vomiting and/or diarrhea, diuretic and/or other concomitant pharmacotherapy, low sodium intake and/or high sodium excretion, and pregnancy.

Lithium's side effects are classified according to whether they are dose-related or non-dose-related (Ereshefsky et al, 1979b).

Dose-Related Side Effects

Dose-related side effects, which are similar to the initial effects experienced during lithium intoxication, are fully reversible with the discontinuation of the drug. The severity of this type of side effect is determined by dosage. In most cases, decreasing dosage is all that is necessary to diminish these unwanted effects.

Gastrointestinal effects

Gastrointestinal side effects are a frequency encountered problem of lithium therapy. These effects include nausea, vomiting, diarrhea, anorexia, and epigastric bloating or pressure, These complaints are common in the first few weeks of therapy, but usually disappear with continued use. When these complaints occur later in the therapy, one should consider lithium toxicity. Their occurrence is dependent on any three factors: (1) irritation of the GI mucosa; (2) the interference of lithium with water and sugar uptake in the GI tract with lead to and osmotic overload in the gut lumen; and (3) a "peaking effect" seen one to three hours after the dose given , affecting the chemo-recepter trigger zone in the medulla. Use of lithium in the capsule form, administration of doses with meals, or an increase in the number of divided doses will alleviate this problem.

Central Nervous System (CNS) Effects

The only CNS symptom that occurs routinely with normal therapeutic levels is a fine hand tremor. It usually begins early in the therapy and frequently disappears with continued use of drug. It can be aggravated by

fatigue, emotional stress, caffeine intake, and concomitantly administered antipsychotic agents. The following should considered when this side effect is significant enough to interfere with work performance : (1) decrease caffeine intake; (2) slightly reduce the lithium dosage; (3) shift a majority of the dose to bedtime; (4) add β-blocking agent, such as propanolol, in a dose of 40 - 80 mg/day (Salem, 1983).

A second CNS symptom, muscular weakness, begins early in the therapy , but was not observed in 100 patients followed up for one to two years while receiving lithium prophylaxis. Thus, no specific treatment appears to be necessary (Salem, 1983).

Other CNS effects,such as lethargy, slurred speech, blurred vision, confusion, ataxia, and nystagmus usually are seen with high serum levels and represent a prodrome associated with impending intoxication ; however, they can occur within the therapeutic range (Salem, Muniz and Director, 1980).

Renal effects

Symptoms of polyuria and thirst can occur, but are generally mild.

Non-Dose-Related Side Effects

These adverse effects are unpredictable and that occur at blood level generally considered non-toxic. Most of the non-dose-related complications are reversible with discontinuation of the drug. However, cessation of lithium treatment is not necessary for mild , persistent side effects.

Neurological effects

Signs of neurotoxicity including confusion, seizures, and acute organic brain syndromes have been reported. Diffuse or focal EEG changes can occur. These lithium-induced neurologic manifestations may occur at therapeutic serum levels. Patients over 55 years old, or those with schizophrenia or preexisting organic brain syndrome, may be slightly more susceptible. Neuropsychological impairment, and more rarely, extrapyramidal symptoms (cogwheel rigidity) have been reported. RBC lithium levels may correlate better with these effects than serum lithium levels.

The neurotoxic effects of lithium that generally occur at high serum concentrations or in patients with the risk factors are associated with increasing signs of cognitive impairment, lassitude, restlessness, and irritability. Although this symptomatology is reversible within 5-10 days , neurotoxicity can progress to frank delirium, ataxia, coarse tremors, seizures and ultimately to coma and death (Lenox and Manji, 1995).

Cardiac effects

The cardiovascular effects of lithium administered orally are rather benign. Most commonly, electrocardiogram recordings demonstrate a flattening and inversion of the T wave. A benign effect that occurs in 20 -30 % of patients who receive lithium, T-wave changes occur in the first few weeks of therapy and continue until drug withdrawal (Salem,1983). Flattening or inverted T-waves, as well as widening of the QRS complex, are

related to the reduction of intracellular potassium induced by lithium (Ereshefsky et al, 1979b).

There are several incidences of sinus node dysfunction or sinoatrail block and ventricular irritability occurring with therapeutic serum lithium levels. Presenting complaints included syncope, difficulty in balance and dyspnea on exertion. The abnormality have been demonstrated to clear when lithium is discontinued and to recur when lithium is reinstitued (Salem,1983).

To prevent these cardiac effects is to (1) obtain a cardiac history from all patients prior to initiation of lithium treatment; (2) in patients over 40 years old and in anyone with a history suggestive of heart disease, a pre treatment ECG should be obtained and reported when symptoms such as palpitations, irregular pulse, or diminished consciousness occur; (3) the use of salt-wasting diuretics or sodium-restricted diets in patient receiving lithium require dosage adjustment and careful monitoring of lithium levels.

Renal Effects

The effects of lithium on the kidney is an issue that must be examined carefully. Lithium is excreted from the body almost entirely from the kidney, with no evidence for any significant protein binding. Lithium reversibly reduce the kidney's ability to concentrate urine primarily through effects on renal tubular function, resulting in the clinical manifestation of polyuria (> 3 L per 24 hours).

Lithium has been implicated as a causative factor in diabetic-insipidus-like syndrome. Related to lithium's ability to inhibit ADH-sensitive adenylcyclase, this complication is of nephrogenic rather than posterior

pituitary origin. The syndrome is not responsive to vasopressin; it must be managed by reduction of the lithium dosage (Ereshefsky et al,1979b).

Effects to Thyroid Gland

Two different problems have been reported secondary to lithium's effect on the thyroid gland in some patients on chronic lithium therapy. Hyperthyroidism is relatively uncommon, while hypothyroidism has been estimated to occur in 4-30 % of patients receiving lithium (Salem, 1983).

Lithium appears to exert antithyroid effects at different levels of thyroid function, including inhibition of hormone synthesis and release, inhibition of the action of TSH and peripheral metabolism of thyroxine (T4). Although reported of lithium-induced hypothyroidism range from 5-38 % due to variability in criteria for diagnosis and sensitivity of laboratory tests, it is estimated that the prevalence of clinical hypothyroidism is more likely 5 % and more common in women (Lenox and Manji, 1995).

These effects of lithium are not a contraindication to therapy, although an elevated TSH over a three- to six-month period implies impaired thyroid reverse, and thyroid hormone replacement is indicated (Salem, 1983).

Many patients have transient alterations of thyroid function. Either discontinuation of lithium therapy or thyroid supplementation (T4) easily corrects this problem in patient who develop clinical signs and symptoms of hypothyroidism (Ereshefsky et al, 1979b).

Before lithium therapy, thyroid function should be evaluated by a serum T4. The diagnosis of hypothyroidism can be suspected if three or more of the following clinical feature exist : extreme fatigue, weight

increase, hair loss, sensitivity to cold, pretibial edema, hoarseness of voice, and coarseness of skin, If hypothyroidism is suspected, a serum T4 and TSH should be measured.

Hyperthyroidism associated with lithium therapy also have reported. Discontinuing the lithium has led to normalization of the thyroid test. If lithium needs to be continued, the hyperthyroid state can be managed by appropriate therapy with propylthiouracil or methimazole (Salem, 1983).

Bone marrow Effects

Lithium can cause leukocytosis in patients secondary to neutropenia with concomitant lymphocytopenia. The elevation is not related to dose nor to serum level of lithium, persists throughout treatment, and is readily reversible upon discontinuation of therapy.

Considering the above evidence, one should obtain a baseline white blood count and thereafter whenever physical symptoms of leukemia, such as fatigue, lassitude, or weakness, develop (Salem, 1983).

Weight Gain

Approximately 30 % of patients on lithium maintenance may gain as much as 5-10 kg. resulting in patient's discontinuation of lithium. This problem can be treated by limitation of caloric intake. A baseline weight and weight measurement every three months will aid in timely intervention with weight reduction techniques (Salem, 1983).

Dermatologic Effects

Dermatologic effects tended to be a rare side effect of lithium ; but there are several reports indicate various dermatologic reactions such as acne,

psoriasis, hair loss, allergic vasculitis and exfoliative dermatitis. Dosage reduction or discontinuation of lithium may alleviate these reactions (Salem, 1983).

Therapeutic Drug Monitoring of Lithium

Therapeutic drug monitoring (TDM) is an important tool when using certain psychotropic drugs. Therapeutic drug monitoring enhances the clinicians ability to rationally adjust the dose of selected medications (e.g.,tricyclic antidepressants, lithium, carbamazepine) to increase therapeutic efficacy and reduce adverse side effects. Therapeutic drug monitoring allows the clinician to identify subtherapeutic plasma concentrations as well as potentially toxic plasma concentrations.

Aims of Therapeutic Drug Monitoring are:

1. To Assess compliance
2. To enhance therapeutic response
3. To avoid toxicity of drug with narrow therapeutic index
4. To minimize cost of treatment
5. To avoid medicolegal problems

After Cade's 1949 report on the therapeutic use of lithium in mania, Talbott used plasma lithium concentrations as a monitoring tool in lithium treatment. In 1951, Noack and Trautner reported no correlation between

clinical effects (including toxicity) and plasma and urine concentration determined at random. They, therefore , saw no utility in monitoring plasma lithium concentrations during lithium therapy (Carson, 1992). At that time clinical pharmacokinetic principles were not generally appreciated and studied. There were not many information in pharmacokinetics to apply in lithium therapy. The blood samples were often obtained at random times following a dose, ensuring that any concentration-effect or concentration-adverse effect relationship would remain obscured. It was gradually recognized that safe lithium treatment required close and periodic observation for side effects, careful patient education, and monitoring of lithium concentration in blood or serum or plasma.

Clinically lithium can be measured in blood, saliva, red blood cells, and tear. In general practice, however, only serum or plasma concentrations are measured because of practical considerations and insufficient data on the correlation of saliva and RBC concentrations to response.

The currently recognized standard draw time for lithium serum concentrations is a trough measured at least 10 to 12 hours after the evening dose . This 12-hour interval has become the standard for therapeutic drug monitoring , as concentrations measured prior to 10 to 12 hours postdose may still be in the absorption and distribution phases (because of variations in the dissolution times of different preparations and the differences in the absorption course among individual patients. Serum concentrations determined 8 hours postdose could be 20 to 25 % higher than if the same sample had been drawn 12 hours postdose. This might lead to the

determination of a therapeutic range higher than necessary. In contrast, samples taken later than 12 hours postdose might be as much as 15 to 20 % lower than when compared with 12-hour samples if drawn as late as 16 hours postdose. The effect would be to indicate a therapeutic range lower than needed for the desired effect (Winter et al., 1992).

Standard Lithium Concentration Assessment for Monitoring Lithium Therapy (Amdisen and Carson,1986) are as follow:

1. The daily dose should be divided into two or more doses.

2. Blood samples should be obtained in the morning before the first dose and 12 hours after the evening dose.

3. The dosage regimen should be carefully monitored at least one day before blood sampling (number of doses taken, timing of doses taken).

4. The samples should be obtained under steady-state conditions (previous therapy constant for at least 7 days).

An analytical method with an accuracy and precision corresponding to a coefficient of variation (CV) of 1 % to 3 % or less is necessary to monitor lithium intoxication and patient noncompliance and to predict the maintenance dose.

The method of choice for determining serum lithium concentrations is photometry. Three methods are available as seen in table V. Atomic emission flame photometry (FP) is by far the most widespread method. Flame atomic absorption spectrophotometry (Flame-AA) is more demanding and less widespread use , although it is equally accurate. The seldom-used and sophisticated method is flameless furnace atomic absorption

spectrophotometry (Furnace-AA). The absorption methods are generally more expensive than the emission methods. The basic principles of these methods is that the lithium content of a test samples is measured against a series of lithium reference samples in an appropriately matched matrix (with regard to background substances and viscosity) to form a standard calibration curve (Carson, 1992).

The ion selective electrode (ISE) technique ,used in this study, measures the lithium ion concentration similar to the way a pH electrode measures hydrogen ions. Generally, the available electrodes for lithium are not as specific as those available for sodium or potassium. Therefore, some ISE assays simultaneously measure sodium and utilize specific correction algorithms to correct for background ion concentrations. The advantages of this assay include rapid speed, low cost, small sample size, ability to measure concentrations in various biological fluids, and portability (Carson, 1992).

Table V Comparison of Lithium Assay Methodologies

Method	Specificity	Sensitivity	Sample volume	Speed	Cost	Difficulty of operation
FP	1	2	25 µL - 2 mL	2	1	1
Flame-AA	2	1	25 µL - 1 mL	1	2	2
Furnace-AA	2	3	1 µL - 0.1 mL	1	2	3-2
ISE	1	1	< 0.1mL	3	1	1

1 = Least

Several other techniques which are unavailable for clinical application include the neutron-activation method and the mass spectrophotometry method, both of which are very accurate but also very expensive. Nuclear magnetic resonance spectrophotometry has been used to measure brain and muscle concentrations of lithium in normal volunteers and bipolar patients. Lithium concentrations can be determined from small volumes (1 to 100 microL) of blood, saliva, and urine with appropriate dilutions and sample preparations.