

PRODUCT MONOGRAPH

Pr LITHMAX®

Lithium Carbonate Sustained-Release Tablets

House Standard

300 mg

Anti-Manic Agent

**AA PHARMA INC.
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THERAPEUTIC CLASSIFICATION

Anti-Manic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Although lithium is useful for its anti-manic effect and in preventing relapses in patients with a clear-cut diagnosis of bipolar affective disorder, it has very little, if any, direct effect on moods, normal or abnormal.

Lithium alters sodium transport in nerve and muscle cells, effects a shift toward intraneuronal metabolism of catecholamines and has an inhibitory action on the intracellular formation of cyclic, AMP. However, the specific biochemical mechanism of action of lithium in mania is still largely unknown.

Use of a sustained-release lithium preparation can reduce the frequency of absorption-related side effects in selected individuals who are particularly sensitive to rapid increases in serum lithium concentrations. However, reduction of absorption-related side effects should not be the only consideration when prescribing lithium for prolonged maintenance therapy. Clinical evidence suggests that the main long-term toxic effect of lithium on the kidney may not be associated with high peak serum lithium levels (as produced by giving immediate-release lithium in a single daily dose), but rather with the presence of sustained, though lower, serum lithium levels (as produced by giving immediate-release lithium in two or three divided doses), which allow no opportunity for

kidney regeneration in a nearly drug-free environment. Therefore, the long-term maintenance of relatively constant serum lithium levels throughout the day, which tends to result from the twice-daily administration of sustained-release preparations, or from multiple daily doses of immediate-release preparations, may not be desirable.

Pharmacokinetics

Lithium is excreted primarily in the urine, and the elimination half-life is approximately 24 hours. Renal lithium clearance tends to be remarkably constant in the same individual but decreases with age or when sodium intake is lowered. The dose necessary to maintain a given concentration of serum lithium depends on the ability of the kidney to excrete lithium. However, renal lithium excretion may vary greatly between individuals, and lithium dosage, therefore, must be adjusted individually. It has been suggested that many patients retain larger amounts of lithium during the active manic phase but recent studies have been unable to confirm a clear difference in excretion patterns; however, patients in a manic state appear to have increased tolerance to lithium.

Comparative Bioavailability

Three comparative bioavailability studies were performed using healthy human volunteers, one under fasted, one under fed and one under steady-state conditions. The rate and extent of absorption of lithium was measured and compared following oral administration 2 x 300 mg (fasting and fed studies) or 1 x 300 mg (steady-state study) of LITHMAX[®] Tablets or Duralith[®] Tablets. The results from measured data are summarized in the following three tables:

| Summary Table of the Comparative Bioavailability Data Lithium Carbonate SR (Dose: 2 x 300 mg) From Measured Data – Under Fasting Conditions Based on Lithium | | | | |
|--|---|-------------------|-----------------------------------|----------------------------------|
| Parameter | Geometric Mean Arithmetic Mean (CV%) | | Ratio of Geometric Means (%)** | 95% Confidence Interval (%)** |
| | Lithmax® | Duralith® † | | |
| AUC _T (µg.h/mL) | 46.1 47.6 (25) | 42.2 43.2 (22) | 109.2 | 99.5 – 119.9 |
| AUC ₀₋₇₂ (µg.h/mL) | 51.8 52.5 (17) | 46.0 46.5 (16) | 112.8 | 104.6 – 121.7 |
| AUC _I (µg.h/mL) | 51.3 53.0 (26) | 46.8 48.1 (23) | 109.6 | 100.3 – 119.8 |
| C _{max} (µg/mL) | 1.98 2.01 (17) | 1.92 1.93 (14) | 103.4 | 96.3 – 111.0 |
| T _{max} * (h) | 5.04 (19) | 4.21 (21) | | |
| T _½ * (h) | 20.5 (21) | 20.9 (21) | | |
| * Arithmetic means (CV%). | | | | |
| ** Based on the least squares estimate. | | | | |
| † Duralith® is marketed by Janssen-Ortho Inc., Toronto, ON Canada. | | | | |

| Summary Table of the Comparative Bioavailability Data Lithium Carbonate SR (Dose: 2 x 300 mg) From Measured Data – Under Fed Conditions Based on Lithium | | | | |
|--|---|-------------------|-----------------------------------|----------------------------------|
| Parameter | Geometric Mean Arithmetic Mean (CV%) | | Ratio of Geometric Means (%)** | 95% Confidence Interval (%)** |
| | Lithmax® | Duralith® † | | |
| AUC _T (µg.h/mL) | 54.3 54.6 (12) | 52.4 53.3 (17) | 103.5 | 99.7 – 107.5 |
| AUC ₀₋₇₂ (µg.h/mL) | 54.3 54.6 (12) | 54.1 54.5 (12) | 101.9 | 99.8 – 104.1 |
| AUC _I (µg.h/mL) | 59.8 60.2 (12) | 58.5 59.4 (16) | 102.2 | 98.6 – 106.0 |
| C _{max} (µg/mL) | 2.86 2.97 (28) | 2.62 2.70 (26) | 109.5 | 99.1 – 121.0 |
| T _{max} * (h) | 5.29 (28) | 5.13 (38) | | |
| T _½ * (h) | 21.8 (13) | 22.6 (13) | | |
| * Arithmetic means (CV%). | | | | |
| ** Based on the least squares estimate. | | | | |
| † Duralith® is marketed by Janssen-Ortho Inc., Toronto, ON Canada. | | | | |

| Summary Table of the Comparative Bioavailability Data Lithium Carbonate SR (Dose: 1 x 300 mg every 12 hours for 7 days) From Measured Data – At Steady State Based on Lithium | | | | |
|--|---|-------------------------|-----------------------------------|----------------------------------|
| Parameter | Geometric Mean Arithmetic Mean (CV%) | | Ratio of Geometric Means (%)** | 95% Confidence Interval (%)** |
| | Lithmax [®] | Duralith [®] † | | |
| AUC _T (µg.h/mL) | 34.5 35.1 (18) | 32.5 33.1 (18) | 106.1 | 101.7 – 110.7 |
| C _{max} (µg/mL) | 3.46 3.52 (16) | 3.33 3.37 (16) | 104.1 | 100.1 – 108.3 |
| C _{min} (µg/mL) | 2.16 2.23 (24) | 2.02 2.08 (24) | 107.1 | 101.1 – 113.4 |
| T _{max} [*] (h) | 3.52 (19) | 3.57 (19) | | |
| Fluctuation [*] (%) | 45.2 (22) | 48.3 (22) | | |
| * Arithmetic means (CV%). | | | | |
| ** Based on the least squares estimate. | | | | |
| † Duralith [®] is marketed by Janssen-Ortho Inc., Toronto, ON Canada. | | | | |

INDICATIONS AND CLINICAL USE

LITHMAX[®] (lithium carbonate sustained-release tablets) is indicated in the lithium treatment of manic episodes of manic-depressive illness. Maintenance therapy has been found useful in preventing or diminishing the frequency of subsequent relapses in bipolar manic-depressive patients (with a history of mania).

Typical symptoms of mania, as an affective disorder, include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity or poor judgment, aggressiveness, and possibly hostility. When given to a patient experiencing a manic episode, lithium may produce a normalization of symptomatology within 1 to 3 weeks.

CONTRAINDICATIONS

LITHMAX[®] (lithium carbonate sustained-release tablets) generally should not be given to patients with significant brain damage, renal or cardiovascular disease, severe debilitation or dehydration, sodium depletion, or to patients receiving diuretics; the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life-threatening and if such a patient fails to respond to other measures, lithium treatment may be undertaken, in selected cases, with extreme caution, including thorough medical assessment and appropriate consultation for at-risk patients, daily serum lithium determinations and adjustments of the doses to levels tolerated by the individual patient. In such instances, hospitalization is a necessity.

WARNINGS

LITHIUM TOXICITY IS CLOSELY RELATED TO SERUM LITHIUM LEVELS AND CAN OCCUR AT DOSES CLOSE TO THE THERAPEUTIC LEVELS. FACILITIES FOR PROMPT AND ACCURATE SERUM LITHIUM DETERMINATIONS SHOULD BE AVAILABLE BEFORE INITIATING THERAPY.

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (see DOSAGE AND ADMINISTRATION).

Impaired Renal Function

Chronic lithium therapy is frequently associated with a decrease in renal concentrating capacity with development of thirst, polyuria, nycturia, weight gain and altered kidney function tests, occasionally presenting as nephrogenic diabetes insipidus. Such patients should be managed carefully to avoid dehydration with resulting lithium retention and toxicity. The evidence suggests

that impaired renal function during chronic therapy may be, in most instances, only partially reversible when lithium is discontinued.

PREVENTION OF RENAL TOXICITY AND OTHER TOXIC EFFECTS OF LONG-TERM THERAPY REQUIRES A FIRM DIAGNOSIS OF BIPOLAR MANIC-DEPRESSIVE ILLNESS; CAREFUL SCREENING FOR PRE-EXISTING RENAL AND OTHER DISEASES; ESTABLISHMENT OF STANDARDIZED 12-HOUR SERUM LITHIUM LEVELS WHICH ARE AS LOW AS POSSIBLE YET CLINICALLY EFFECTIVE; MAINTAINING CONTROL OF TREATMENT BY MONITORING SERUM LITHIUM LEVELS AND EXERCISING CLINICAL AND LABORATORY SURVEILLANCE OVER POSSIBLE SIDE EFFECTS OR SIGNS OF LITHIUM INTOXICATION; EXERCISING MAXIMUM CONTROL OF AT-RISK PATIENTS; ENSURING THAT LONG-TERM LITHIUM THERAPY IS MAINTAINED ONLY WHEN CLINICAL RESPONSE HAS BEEN CLEARLY ESTABLISHED; AND ADJUSTING THE DOSAGE SCHEDULE AND PREPARATION USED SO AS TO OBTAIN TEMPORARILY PERIODS OF LITHIUM CONCENTRATIONS AS LOW AS POSSIBLE IN THE KIDNEY.

Glomerular sclerosis and interstitial fibrosis, as well as tubular lesions, have been reported in patients on chronic lithium therapy.

When kidney function is assessed for baseline data prior to starting lithium therapy or thereafter, routine urinalysis and other tests may be used to evaluate tubular function (e.g. urine specific gravity or osmolality or 24-hour urine volume) and glomerular function (e.g. serum creatinine or creatinine clearance).

DURING LITHIUM THERAPY, PROGRESSIVE OR SUDDEN CHANGES IN RENAL FUNCTION, EVEN WITHIN THE NORMAL RANGE, INDICATE THE NEED FOR RE-EVALUATION OF

TREATMENT, INCLUDING DOSAGE AND FREQUENCY OF LITHIUM ADMINISTRATION, AND A RE-ASSESSMENT OF THE RISK-BENEFIT OF LONG-TERM LITHIUM THERAPY.

Use During Pregnancy or Child-Bearing Age

Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly; nephrogenic diabetes insipidus, euthyroid goiter and hypoglycemia have occurred in infants born to women who took lithium during pregnancy. Therefore, lithium should not be used during pregnancy or in women of childbearing potential unless it cannot be substituted by other appropriate therapy and, in the opinion of the physician, the expected benefits outweigh the possible hazards to the fetus (see TOXICOLOGY - Reproductive Studies).

Use in Nursing Mothers

Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazards to the child.

Pediatric Use

Since information regarding the safety and effectiveness of lithium in children less than 12 years of age is not available, the use of lithium carbonate sustained-release tablets in such patients is not recommended at this time.

Parathyroid Abnormalities:

A systematic review and meta-analysis indicates that about 10% of patients on long-term lithium therapy may develop hypercalcemia with or without hyperparathyroidism. Screening of serum calcium level and if necessary serum parathormone level need to be considered.

PRECAUTIONS

TO MAXIMIZE BENEFITS, MINIMIZE THE RISKS, AND REDUCE AS MUCH AS POSSIBLE THE ADVERSE EFFECTS OF LITHIUM THERAPY, IT IS ESSENTIAL TO PROVIDE PROPER INFORMATION TO PATIENTS AND RELATIVES ABOUT THE TREATMENT REGIMEN AND CONTROL PROCEDURES REQUIRED DURING TREATMENT, AS WELL AS AN EXPLANATION OF THE EXPECTED BENEFITS AND THE MOST COMMONLY EXPERIENCED IMMEDIATE AND LONG-TERM SIDE EFFECTS. APPROPRIATE WRITTEN MATERIAL SHOULD BE PROVIDED TO SUPPLEMENT VERBAL INFORMATION.

Outpatients and their families should be warned that the patient must discontinue therapy with lithium carbonate sustained-release tablets and contact the physician if clinical signs of lithium toxicity such as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur. Furthermore, since lithium may impair mental and/or physical abilities, patients should be cautioned about undertaking activities requiring alertness (e.g. operating vehicles or machinery).

Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium therapy; where hypothyroidism exists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters, if any. Where

hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

Lithium decreases sodium re-absorption by the renal tubules, which would lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2500-3000 mL), at least during the initial stabilization period. Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if these occur, supplemental fluid and salt should be administered. In addition to sweating and diarrhea, concomitant infection, with elevated temperatures, may also necessitate a temporary reduction or cessation of medication.

Drug Interactions

Combined Use of Haloperidol and Lithium

An encephalopathy resembling malignant neuroleptic syndrome (characterized by weakness; lethargy; fever; tremulousness and confusion; extrapyramidal symptoms; leukocytosis; and elevated serum enzymes, BUN and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and concomitant administration of lithium and haloperidol has not been clearly established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity, such as rigidity and/or hyperpyrexia, and treatment discontinued promptly if such signs appear.

Combined Use of Phenothiazines and Lithium

Both pharmacokinetic interactions and clinical toxicity with the combined use of these agents have been described. Lithium-induced reductions in plasma chlorpromazine levels, phenothiazine-induced increases in the red cell uptake of lithium, and chlorpromazine-induced increases in renal lithium excretion have been reported. Clinically, occasional cases of neurotoxicity have been reported and may be more likely to occur with thioridazine than other phenothiazines when combined with lithium. Therefore, the clinician should be alert for altered response to either drug when used in combination and when either drug is withdrawn.

Other Considerations

The action of neuromuscular blocking agents may be prolonged in patients receiving lithium. Therefore, caution should be exercised when the combination is required. A temporary omission of a few doses of lithium can reduce the risks of this interaction.

Indomethacin has been reported to increase steady-state plasma lithium levels by 30 to 59%. There is also evidence that other non-steroidal anti-inflammatory agents may have a similar effect. When such combinations are used, increased frequency of monitoring plasma lithium levels is recommended.

There are reports that concurrent use of methyldopa or tetracycline may increase the risk of lithium toxicity.

Concurrent use of lithium and carbamazepine or phenytoin might result in an increased risk of central nervous system toxicity.

The administration of aminophylline or theophylline to patients on lithium therapy may require increased lithium doses to maintain the psychotropic effect.

Patients stabilized on lithium therapy who receive a thiazide diuretic may require a reduction of lithium dosage to avoid accumulation and toxicity, since there is often a 20 to 40% reduction of renal lithium clearance. Furosemide appears to be less likely to affect lithium clearance.

Parathyroid Disorders: Hypercalcemia with or without hyperparathyroidism has been reported in patients on lithium therapy. Screening of serum calcium level and if necessary serum parathormone level need to be considered.

ADVERSE REACTIONS

Mild side effects may be encountered even when serum lithium levels remain below 1 mEq/L.

The most frequent side effects are the initial post-absorptive symptoms, believed to be associated with a rapid rise in serum lithium levels. They include nausea, abdominal pain, vomiting, diarrhea, vertigo, muscle weakness, sleepiness and a dazed feeling, and they frequently disappear after stabilization of therapy. The more common and persistent adverse reactions are fine tremor of the hands (which is not responsive to antiparkinson drugs) and, at times, fatigue, thirst and polyuria (renal toxicity). These side effects may subside with continued treatment, or a temporary reduction or cessation of dosage. If persistent, a lowering or cessation of dosage and re-assessment of lithium therapy is indicated.

Mild to moderate toxic reactions may occur at lithium levels from 1.5 to 2 mEq/L, and moderate to severe reactions at levels above 2 mEq/L. Permanent neurological damage has been reported after exposure to toxic levels of lithium.

A number of patients may experience lithium accumulation during initial therapy, increasing to toxic levels and requiring immediate discontinuation of the drug. Some elderly patients with lowered renal clearances for lithium may also experience different degrees of lithium toxicity, requiring reduction or temporary withdrawal of medication. However, in patients with normal renal clearance the toxic manifestations appear to occur in a fairly regular sequence related to serum lithium levels. The usually transient GI symptoms are the earliest side effects to occur. A mild degree of fine tremor of the hands may persist throughout therapy. Thirst and polyuria may be followed by increased drowsiness, ataxia, tinnitus and blurred vision, indicating early intoxication. As intoxication progresses the following manifestations may be encountered: confusion, increasing disorientation, muscle twitching, hyperreflexia, nystagmus, seizures, diarrhea, vomiting, and eventually coma and death.

The following toxic reactions have been reported and appear to be related to serum lithium levels, including levels within the therapeutic range.

Neuromuscular

Tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), ataxia, choreoathetotic movements, hyperactive deep tendon reflexes.

Central Nervous System

Blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma.

Cardiovascular

Cardiac arrhythmia, hypotension, peripheral circulatory collapse.

Gastrointestinal

Anorexia, nausea, vomiting, diarrhea.

Genitourinary

Albuminuria, oliguria, polyuria, glycosuria.

Dermatologic

Drying and thinning of hair, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, alopecia and exacerbation of psoriasis.

Autonomic Nervous System

Blurred vision, dry mouth.

Thyroid Abnormalities

Euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T_3 and T_4 levels and elevated TSH. Iodine¹³¹ uptake may be elevated. On the average, 5 to 15% of patients on long-term lithium therapy manifest clinical signs or have altered serum hormone levels (see PRECAUTIONS). Paradoxically, rare cases of hyperthyroidism have been reported.

EEG Changes

Diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm.

ECG Changes

Reversible flattening, isoelectricity or inversion of T waves.

Miscellaneous

Fatigue, lethargy, transient scotomata, dehydration, weight loss, tendency to sleep.

Miscellaneous Reactions Frequently Unrelated to Dosage

Transient electroencephalographic and electrocardiographic changes, leukocytosis, headache, diffuse non-toxic goiter with or without hypothyroidism, transient hyperglycemia, generalized pruritus with or without rash, cutaneous ulcers, albuminuria, worsening of organic brain syndrome, excessive weight gain, edematous swelling of ankles or wrists, and thirst or polyuria sometimes resembling diabetes insipidus, and metallic taste.

A single instance has been reported of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of the starting of treatment with lithium. The mechanism through which these symptoms (resembling Raynaud's syndrome) developed is not known. Recovery followed discontinuance.

Serious Reactions to Long-term Therapy

In addition to other possible adverse reactions, the main concern during chronic lithium therapy centres on kidney function, the thyroid, parathyroid, the bones and the skin.

SYMPTOMS AND TREATMENT OF OVERDOSE

The toxic levels for lithium are close to the therapeutic levels. It is therefore important that patients and their families be cautioned to watch for early symptoms of overdosage and to discontinue lithium carbonate sustained-release tablets and inform the physician should they occur. Early signs of toxicity which may occur at serum lithium levels lower than 2 mEq/L were described under ADVERSE REACTIONS and usually respond to reduction of dosage. Lithium intoxication has been preceded by the appearance or aggravation of the following symptoms: sluggishness, drowsiness, lethargy, coarse tremors or muscle twitchings, loss of appetite, vomiting and diarrhea. Occurrence of these symptoms requires immediate cessation of medication and careful clinical re-assessment of management. Signs and symptoms of lithium intoxication have already been described under ADVERSE REACTIONS.

Treatment

No specific antidote for lithium poisoning is known. Early symptoms of lithium toxicity can usually be treated by reduction in the dosage or cessation of the drug and resumption of treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient and supportive care.

Recommended treatment consists of: 1) gastric lavage, 2) correction of fluid and electrolyte imbalance and 3) regulation of kidney function. Urea, mannitol and aminophylline all produce

significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. Infection prophylaxis, regular chest x-ray, and preservation of adequate respiration are essential.

DOSAGE AND ADMINISTRATION

Selection of Patients and Approach to Lithium Therapy

The results of lithium therapy depend largely on the nature and course of the illness itself, rather than on the symptoms. The selection of patients for long-term treatment requires a clear-cut diagnosis of primary affective disorder, the condition for which the stabilizing effects of lithium have been found useful. The variables that have been more consistently associated with response to lithium therapy in patients with a primary affective disorder are: the good quality of remissions with good function and no significant symptomatology during the free intervals between previous episodes of illness; low frequency of episodes, typically one or two (and not more than three or four) per year; and symptomatology during the acute episodes that meet strict criteria for a primary affective disorder (DSM-III; Research Diagnostic Criteria).

Screening for lithium candidates should include at least a medical history and physical examination with emphasis on the urinary, cardiovascular, gastrointestinal, endocrine and central nervous systems, and the skin. It should also include routine 24-hour urine volume, serum creatinine, record of weight, an ECG, possibly electrolytes and TSH, and for long-term treatment, creatinine clearance and a urine concentration test. Other examinations and tests should be used when indicated. Monitoring lithium treatment should include, for each visit, mental status, physical examination, weight, 12-hour serum lithium and a check for lithium side effects and compliance. It should also include serum creatinine every 2 months, plasma thyroid hormone and TSH every 6 to 12 months (particularly in female patients) and attention to renal and thyroid function should be

maintained throughout, with tests used for baseline screening repeated, as required. Also, consider serum calcium level before onset of treatment, after 6 months, and yearly thereafter in long-term treatment.

The first objective of treatment is to establish an effective and safe daily dosage of lithium, with the aid of standardized 12-hour serum lithium levels, maintained within the therapeutic range, as high as necessary for efficacy, and with the patient as much as possible free of significant side effects. Two daily doses should be used initially, at least until the daily dosage is established. The next aim is to move to an optimal dose, which should be as low as possible, consistent with protection against relapse. During follow-up, an adjustment to lower dosages may be required to minimize adverse effects, and a change in the lithium preparation used and/or the frequency of dosing, either towards multiple doses or towards a single dose, may be necessary to handle absorption-related adverse effects or concern over possible renal toxicity. Intermittent lithium treatment in carefully selected patients has been recommended by some lithium experts, but should not be undertaken without careful planning and great caution. The co-operation of patients and relatives is required throughout.

Before deciding on the institution of long-term treatment, it is essential to establish that the patient has clearly responded to a course of stabilizing lithium therapy and that the risk of such therapy is acceptable. Maintaining a patient with a lithium non-responsive condition on long-term therapy poses an unacceptable risk. A decision with regards to long-term therapy can be made during a time-limited trial of lithium therapy with frequent re-assessment of outcome. The following are among the factors to be re-assessed before a decision is made: careful reconfirmation of the diagnosis of primary affective disorder; the health status of the patient; the side effects of lithium therapy experienced by the patient; and the response to treatment. Assessment of response to treatment is based strictly on firm evidence of relapse prevention during a reasonable trial period,

but can be assisted by consideration of the predictors of response outlined above. Great pains should be taken to exclude false responders and false non-responders. It should also be borne in mind that non-responders are more susceptible to the adverse effects of lithium.

Acute Mania

The therapeutic dose for the treatment of acute mania should be based primarily on the patient's clinical condition. It must be individualized for each patient according to blood levels and clinical response. Manic patients usually require serum lithium levels in excess of 1 mEq/L and the dosage should be adjusted to obtain serum levels between 1 and 1.5 mEq/L (in blood samples drawn before the patient has had his first lithium dose of the day).

In properly screened adult patients with good renal function, the suggested initial dosage for acute mania is 1200 to 1800 mg (approximately 50 mEq/L) divided into 2 doses and administered at 12-hour intervals. In view of the large variability of renal lithium excretion among individuals, it is suggested that lithium treatment be started at a dose between 600 and 900 mg/day, reaching a level of 1200 to 1800 mg/day, in 2 divided doses, on the second day.

Depending on the patient's clinical condition, the initial dosage should be adjusted to produce the desired serum lithium level. The weight of the patient should also influence the choice of the initial dose. Lithium should be used cautiously and in reduced doses in the elderly patient, usually in the range of 600 to 1200 mg/day or less, starting with smaller doses (see also WARNINGS and PRECAUTIONS). Serum lithium levels must always be checked carefully and frequently during initiation of treatment, monitored regularly thereafter and should be kept below 1.5 mEq/L.

Maintenance Therapy

After the acute manic episode subsides, usually within a week, the dosage should be rapidly reduced to achieve serum levels between 0.6 and 1.2 mEq/L, since there is evidence of a decreased tolerance to lithium at this time. The average suggested dosage at this stage is 900 mg/day (approximately 25 mEq) administered in a single dose at bedtime, with a range usually between 600 and 1200 mg/day. If a satisfactory response is not obtained within 14 days, lithium therapy should be discontinued. When the manic attack is controlled, lithium administration should be maintained for the expected duration of the manic phase, since early withdrawal might lead to relapse. Long-term lithium treatment has been found useful for relapse prevention (see DOSAGE AND ADMINISTRATION, Selection of Patients and Approach to Lithium Therapy). It is essential to maintain clinical supervision of the patient and to monitor serum lithium levels as required during treatment (see WARNINGS and PRECAUTIONS). Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every 2 months.

Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels of 1.0 to 1.4 mEq/L. Elderly patients often respond to reduced dosage and may exhibit signs of toxicity at serum levels ordinarily tolerated by other patients.

Lithium carbonate sustained-release tablets should be swallowed whole or broken in half.

They should not be chewed or crushed.

N.B.: Blood samples for serum lithium determination should be drawn prior to the next dose and when lithium concentrations are relatively stable (i.e. 10 to 14 hours after the previous dose of lithium). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical assessment and laboratory analyses.

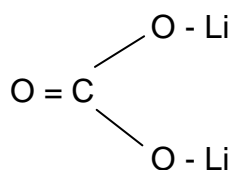
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Lithium carbonate

Chemical Name: Carbonic acid, dilithium salt

Chemical Structure:



Molecular Formula: Li_2CO_3

Molecular Weight: 73.89

Description: White, granular, odourless powder sparingly soluble in water, very slightly soluble in alcohol, dissolves with effervescence in dilute acid. Saturated solution is alkaline to litmus.

Composition

In addition to lithium carbonate, each sustained release tablet contains the non-medicinal ingredients hydroxypropyl methylcellulose and magnesium stearate.

Stability and Storage Recommendations

LITHMAX® tablets should be stored between 15-30°C.

AVAILABILITY OF DOSAGE FORMS

LITHMAX® (lithium carbonate sustained release tablets): each round, white, flat-faced, beveled-edge tablet, scored and engraved "LIT" over "300" on one side and plain on the other, contains 300 mg of lithium carbonate. Available in bottles of 100. Lithium carbonate is a prescription drug.

PHARMACOLOGY

The active ingredient in LITHMAX® tablets is lithium carbonate.

Lithium is inactive in most psychopharmacological screening tests but it does produce marked potentiation of amphetamine hyperactivity in animals. It does not appear to protect against the action of stimulant and convulsive drugs and produces only slight potentiation of CNS depressants.

Lithium can replace sodium in extracellular fluid and during the process of depolarization it has an extremely rapid intracellular influx. However, it is not effectively removed by the sodium pump, thereby preventing the cellular re-entry of potassium. As a result, it interferes with electrolyte distribution across the neuronal membrane, leading to a fall in membrane potential and changes in conduction and neuronal excitability. In humans, lithium alters the excitability of the CNS as measured by cortical-evoked potentials.

Balance studies indicate that lithium may produce a transitory diuresis with increase in sodium and potassium excretion. A period of equilibrium or slight retention may follow but persistent polyuria may occur in some patients. There is evidence that therapeutic doses of lithium decrease the 24-hour exchangeable sodium. Longitudinal metabolic studies have demonstrated cumulative lithium retention in some patients without undue rise in plasma lithium values, indicating a

possible intracellular retention of lithium. There is some evidence that lithium may affect the metabolism of potassium, magnesium and calcium.

There is also evidence to indicate that lithium might produce a shift in norepinephrine metabolism from O-methylation to intraneuronal deamination, as evidenced by a decrease in normetanephrine and an increase in deaminated catechols observed in animal studies. This would suggest that lithium may decrease levels of norepinephrine available at the central adrenergic receptors. It would appear, however, that this action is not specific of lithium. Lithium may also alter the metabolism of other monoamines such as serotonin.

ECG changes with lithium have been reported in both animals and human.

The mechanism whereby lithium controls manic episodes and possibly influences affective disorders is not yet known.

Unlike other anti-manic agents, it does not possess general sedative properties. There is evidence, however, that lithium alters sodium transport and may interfere with the ion exchange mechanism and nerve conduction. Fluid and electrolyte metabolism are believed to be altered in affective disorders and this may be related to the therapeutic action of lithium. It also has been suggested that lithium may decrease norepinephrine levels at critical receptor sites in the brain where this catecholamine is presumed to be increased during mania.

Special Studies

1. A crossover multi-dose bioavailability study involving substituting lithium carbonate sustained-release tablets b.i.d. for regular lithium administered t.i.d. in the same total daily dosage for 5

days in manic patients previously stabilized with optimum therapeutic doses of regular-release lithium, showed that the area under the 24-hour plasma level curve (AUC) for lithium carbonate sustained-release tablets was 90% of that for the regular-release lithium. The peak for regular-release lithium was 10-20% higher than that for sustained-release tablets ($p < 0.01$) and the time to peak was greater for sustained-release tablets ($p < 0.01$) compared to the regular-release product. The variability in plasma level over the 24-hour period was significantly greater (~40%) for the regular-release product compared to sustained-release tablets (the ratio of the ranges averaging 1.428:1, $p < 0.01$).

Furthermore, the number of hours during the 24-hour period in which the plasma level was in the toxic range (in excess of 1.5 mEq/L) was significantly higher for the regular-release tablet than for sustained-release tablets (2.31 hours regular lithium vs. 0.98 hours lithium carbonate sustained-release tablets, $p < 0.01$).

2. In a double-blind crossover pharmacokinetic comparison study, sustained-release lithium carbonate (300 mg tablets) and regular-release lithium carbonate (300 mg capsules) were administered once a day for 2 weeks to patients with primary bipolar affective disorder who were previously stabilized at a constant dose of lithium. The study dosage for each patient was adjusted to be equal to the maintenance dose of the previous lithium medication. The plasma concentration-time curves from 10.5 to 23 hours post last-dose showed little difference either between the two treatments or between the order of treatment, and the lithium ‘trough’ levels were statistically similar after the 2 weeks of once-a-day lithium administration, for both treatments.

TOXICOLOGY

The acute oral LD₅₀ of lithium carbonate in the rat is 635 mg/kg and in the mouse 650 mg/kg.

Subacute toxicity studies indicate that lithium accumulates faster, and death occurs earlier, in rats and dogs fed low sodium diets. Dogs given 20 mg/kg/day of lithium chloride showed no signs of toxicity when fed a normal salt diet, but died in 2-4 weeks when fed a low sodium diet. Similar results occurred in rats. The signs of toxicity consisted of tremors, lethargy, salivation, vomiting, diuresis, bloody diarrhea, anorexia, emaciation and coma. ECG changes similar to those produced by potassium intoxication were observed. Animals protected by a high sodium intake developed only polyuria. Serum lithium rose gradually in the animals developing signs of toxicity, while serum potassium levels remained fairly constant. In the final stages, serum lithium values rose rapidly as a result of irreversible renal damage, and in the terminal stages hyperkalemia and azotemia were recorded.

The principal toxic effects of lithium are on the kidney, with lesions in the distal convoluted tubules of dogs and in the proximal convoluted tubules of rats. The primary toxic effects in humans appear to be on the central nervous system.

The long-term toxicity of lithium has not yet been tested in animal studies.

Reproductive Studies

Lithium salts influenced the embryonal development of sea urchins, mollusks, amphibians and chicken embryos.

Adverse effects on reproduction have also been reported in mammalian species.

Adverse effects on the number of corpora lutea, percentage of resorptions, embryonic viability and weaning weight in rats, the number of implantation sites in rabbits and the birth weights in

monkeys, have occurred in lithium studies. Cleft palate, together with ocular and auricular defects, occurred in the offspring of mice and rats treated with lithium at doses that produced blood levels similar to the therapeutic range in man.

Lithium decreases the fertility of male rats and is spermicidal *in vitro* for human and animal spermatozoa.

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