LITHANE- lithium carbonate tablet
Miles Pharmaceuticals

LITHANE®
(lithium carbonate)
TABLETS
For Control of Manic Episodes in Manic-Depressive Psychosis

WARNING

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.

DESCRIPTION

Lithium carbonate is a white, light, alkaline powder with molecular formula Li_2CO_3 and molecular weight 73.89. Lithium is an element of the alkali-metal group with atomic number 3, atomic weight 6.94, and an emission line at 671 nm on the flame photometer.

Inert ingredients are: Blue 1 Lake; dibasic calcium phosphate; magnesium stearate; polyethylene glycol; sodium lauryl sulfate; starch; Yellow 5 Lake.

ACTIONS

Preclinical studies have shown that lithium alters sodium transport in nerve and muscle cells and effects a shift toward intraneuronal metabolism of catecholamines, but the specific biochemical mechanism of lithium action in mania is unknown.

INDICATIONS

Lithium carbonate is indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.

Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, 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.

WARNINGS

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation or dehydration, or sodium depletion, and to patients receiving diuretics, since 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 with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued.

Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal functional and morphologic changes and their association with lithium therapy have not been established.

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 following a period of water deprivation, 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 reevaluation of treatment.

Lithium therapy has been reported in some cases to be associated with morphologic changes in the kidneys. The relationship between such changes and renal function has not been established.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, 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 the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. The possibility of similar adverse interactions with other antipsychotic medication exists.

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels (see DOSAGE AND ADMINISTRATION).

Outpatients and their families should be warned that the patient must discontinue lithium carbonate therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur.

Lithium carbonate may impair mental and/or physical abilities. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

Usage in Pregnancy

Adverse effects on nidation in rats, embryo viability in mice, and metabolism *in vitro* of rat testis and human spermatozoa have been attributed to lithium, as have teratogenicity in sub-mammalian species and cleft palates in mice. Studies in rats, rabbits, and monkeys have shown no evidence of lithium-induced teratology.

In humans, lithium carbonate may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are lithium birth registries in the United States and elsewhere; however there is at the present time insufficient data to determine the effects of lithium carbonate on human fetuses. Therefore, at this point, lithium should not be used in pregnancy, especially the first trimester, unless in the opinion of the physician, the potential benefits outweigh the possible hazards.

Usage 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.

Usage in Children

Since information regarding the safety and effectiveness of lithium carbonate in children under 12 years of age is not available, its use in such patients is not recommended at this time. There has been a report of a transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg child who ingested 300 mg of lithium carbonate.

PRECAUTIONS

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

Drug Interactions

Caution should be used when lithium and diuretics or angiotensin converting enzyme (ACE) inhibitors are used concomitantly because sodium loss may reduce the renal clearance of lithium and increase serum lithium levels with risk of lithium toxicity. When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring of lithium plasma levels is recommended.

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The half-life of elimination of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could 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 such 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.

Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium treatment; 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.

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the over-all incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Indomethacin and piroxicam have been reported to increase significantly, steady state plasma lithium levels. In some cases lithium toxicity has resulted from such interactions. There is also some evidence that other nonsteroidal, anti-inflammatory agents may have a similar effect. When such combinations are used, increased plasma lithium level monitoring is recommended.

ADVERSE REACTIONS

Adverse reactions are seldom encountered at serum lithium levels below 1.5 mEq./l., except in the occasional patient sensitive to lithium. Mild to moderate toxic reactions may occur at levels from 1.5–2.5 mEq./l., and moderate to severe reactions may be seen at levels from 2.0–2.5 mEq./l., depending upon individual response to the drug.

Fine hand tremor, polyuria, and mild thirst may occur during initial therapy for the acute manic phase, and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration.

These side effects are an inconvenience rather than a disabling condition, and usually subside with

continued treatment or a temporary reduction or cessation of dosage. If persistent, a cessation of dosage is indicated.

Diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination may be early signs of lithium intoxication, and can occur at lithium levels below 2.0 mEq./l. At higher levels, giddiness, ataxia, blurred vision, tinnitus, and a large output of dilute urine may be seen. Serum lithium levels above 3.0 mEq./l. may produce a complex clinical picture involving multiple organs and organ systems. Serum lithium levels should not be permitted to exceed 2.0 mEq./l. during the acute treatment phase.

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

Neurological: Cases of pseudotumor cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs.

Neuromuscular: tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), ataxia, choreo-athetotic 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, acute dystonia, and downbeat nystagmus.

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, 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. I^{131} iodine uptake may be elevated. (See Precautions.) Paradoxically, rare cases of hyperthyroidism have been reported.

EEG. Changes: diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm.

EKG. Changes: reversible flattening, isoelectricity or inversion of T-waves.

Miscellaneous: fatigue, lethargy, tendency to sleep, dehydration, weight loss, transient scotomata.

Miscellaneous reactions unrelated to dosage are: transient electroencephalographic and electrocardiographic changes, leucocytosis, headache, diffuse non-toxic goiter with or without hypothyroidism, transient hyperglycemia, generalized pruritus with or without rash, cutaneous ulcers, albuminuria, worsening of organic brain syndromes, excessive weight gain, edematous swelling of ankles or wrists, and thirst or polyuria, sometimes resembling diabetes insipidus, and metallic taste. A single report has been received of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of the starting of treatment of lithium. The mechanism through which these symptoms (resembling Raynaud's Syndrome) developed is not known. Recovery followed discontinuance.

DOSAGE AND ADMINISTRATION

Acute Mania

Optimal patient response to lithium carbonate usually can be established and maintained with 600 mg t.i.d. Such doses will normally produce an effective serum lithium level ranging between 1.0 and 1.5 mEq./l. Dosage must be individualized according to serum levels and clinical response. Regular

monitoring of the patient's clinical state and of serum lithium levels is necessary. Serum levels should be determined twice per week during the acute phase, and until the serum level and clinical condition of the patient have been stabilized.

Long term Control

The desirable lithium levels are 0.6 to 1.2 mEq./l. Dosage will vary from one individual to another, but usually 300 mg t.i.d. or q.i.d will maintain this level. Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every two months.

Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels of 1.0 to 1.5 mEq./l. Elderly patients often respond to reduced dosage, and may exhibit signs of toxicity at serum levels ordinarily tolerated by other patients.

N.B.

Blood samples for serum lithium determinations should be drawn immediately prior to the next dose when lithium concentrations are relatively stable (i.e., 8–12 hours after the previous dose). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical and laboratory analysis.

OVERDOSAGE

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 toxic symptoms and to discontinue the drug and inform the physician should they occur. Toxic symptoms are listed in detail under ADVERSE REACTIONS.

Treatment

No specific antidote for lithium poisoning is known. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the 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 organism.

Treatment is essentially the same as that used in barbiturate poisoning: 1) lavage, 2) correction of fluid and electrolyte imbalance, and 3) regulation of kidney functioning. 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-rays, and preservation of adequate respiration are essential.

HOW SUPPLIED

Lithane (lithium carbonate) is available as scored tablets containing 300 mg of lithium carbonate in bottles of 100 (NDC 0026-2951-51), and 1000 (NDC 0026-2951-54).

Manufactured for
Miles Pharmaceuticals
Division of Miles Laboratories, Inc.
West Haven, Connecticut 06516 USA
by Pfizer Inc., New York, N.Y. 10017

LAB-0140-2.0

LITHANE
lithium carbonate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0026-2951
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
lithium carbonate (UNII: 2BMD2GNA4V) (lithium - UNII:)		300 mg

Inactive Ingredients	
Ingredient Name	**Strength**
Blue 1 Lake ()	
dibasic calcium phosphate ()	
magnesium stearate (UNII: 70097M6I30)	
polyethylene glycol ()	
sodium lauryl sulfate (UNII: 368GB5141J)	
starch ()	
Yellow 5 Lake ()	

Product Characteristics			
Color	GREEN (GREEN)	**Score**	2 pieces
Shape	ROUND (convex)	**Size**	10mm
Flavor		**Imprint Code**	Miles;951
Contains			
Coating	false	**Symbol**	false

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0026-2951-51	100 in 1 BOTTLE		
2	NDC:0026-2951-54	1000 in 1 BOTTLE		

Labeler - Miles Pharmaceuticals

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