Lithium Therapy and Toxicity

RICHARD C. W. HALL, M.D., MARK PERL, M.B.B.S. and BETTY PFEFFERBAUM, M.D.
The University of Texas Medical School, Houston, Texas

Lithium is a potent agent for the control of psychiatric disease. It is safe and effective when properly administered; however, its use requires a maximally informed physician and careful clinical monitoring of patients. The drug's side effects are usually dose related, and certain patients are at greater risk of experiencing toxicity than others. Management of acute intoxication involves gastric lavage, sodium replacement and the administration of other agents or dialysis to facilitate clearance.

Lithium carbonate is the drug of choice for control of manic-depressive illness, manic type. Patients with this illness typically present with pressured speech, reduced need for sleep, hyperactive behavior, grandiosity, elation, flight of ideas, impaired judgment, aggressiveness and, when confronted, hostility. These patients frequently have several episodes of this characteristic behavior and, at times, have alternating periods of profound depression. Lithium carbonate reverses these symptoms within one to three weeks. It has been shown to reduce or prevent regular periodic manic attacks, reduce the emotional and motor hyperactivity of manic patients, increase the time between manic attacks and shorten the duration of manic episodes. The drug is effective in more than 90 percent of patients with typical mania and in about 60 percent of those with atypical manic episodes. The usual time lag from the initial dose of lithium to the remission of mania is six to 10 days, but it may be as long as three weeks.

Other Uses for Lithium

Lithium may also be effective in preventing recurrences of manic-depressive illness of the depressed type. This use of the drug is currently under active investigation, and its efficacy remains to be proved. When lithium is used to control mania, it does not blunt intellectual function or produce a drug-like state.

Current evidence suggests that lithium may be useful for treating some patients with schizo-affective schizophrenia, particularly when given in combination with antipsychotics. Considerably more work needs to be done to identify those schizophrenic patients who will benefit from long-term lithium treatment.

Some epileptic patients show a statistically significant decrease in seizure frequency as well as improved behavior when treated with lithium. In up to 60 percent of a series of epileptics, the drug was reported to reduce the frequency of seizures, "normalize" the electroencephalogram and improve the behavioral patterns of patients between seizures. It may be useful in the control of treatment-resistant temporal lobe epilepsy. It should be noted, however, that a few epileptic patients experience an increased number of seizures while on the medication.

Other conditions for which lithium has not been proved to be of value but may be helpful include aggressive states, cyclothymic personality disorders, hyperactivity in children of lithium-responsive parents, alcoholism, Huntington's chorea, hyperkinesis due to levodopa therapy and tardive dyskinesia. In addition, lithium has been suggested for trial and evaluation as a treatment for premenstrual tension, obsessive-compulsive personality and periodic psychosis; however, current data would not support its routine use in these conditions.

Administration of Lithium Carbonate

The ratio of therapeutic to toxic dose of lithium is narrow. Careful evaluation is necessary before beginning treatment and should include a detailed physical examination, urinalysis, complete blood count, thyroid function tests, renal function tests

(BUN, creatinine and creatinine clearance) and electrocardiogram.

Blood levels generally considered optimal for the management of manic patients range from 0.8 to 1.2 mEq. per L. and are usually achieved by total daily dosages of 900 to 1,200 mg. of lithium. Acutely manic patients often require higher serum levels for initial therapeutic response. For these patients, a loading dose of 1,500 to 1,800 mg. can be given for the first few days of treatment; the dosage can then be adjusted downward on the third or fourth day. As the patient's mania abates, it is crucial that the physician realize that the acute maintenance dose will need to be lowered. Conversely, a patient who is well regulated on prophylactic lithium therapy will require an increase in dosage if a manic attack begins.

The method of administration will alter the serum values. It is best to administer the drug on a divided dosage schedule, *e.g.*, three to four times a day initially. Once a steady state is achieved, twice-daily doses are possible. Blood samples should be drawn 12 hours after administration of the last dose of lithium. (They should never be drawn under eight hours after administration.) If medication has been given as a single bedtime dose, blood levels will be 20 to 30 percent higher than those obtained with a divided dosage schedule. Samples must be drawn at the same time each day if results are to be compared.

During the initial phases of treatment, lithium levels should be monitored at least three times a week. Once a steady state is achieved, serum monitoring every two to four weeks is adequate for the first six months. Thereafter, serum levels can be monitored four times a year.

Current research suggests that the intracellular red blood cell lithium level may be a more sensitive indicator of clinical efficacy than serum lithium levels. However, this is still a research technique. Red blood cell monitoring should be employed, if possible, in a patient who appears refractory to lithium treatment despite adequate serum levels.

What to Tell the Patient on Lithium

Because of the close therapeutic to toxic index of lithium, it is essential that the patient be informed of possible side effects. It is also essential that the patient's family be aware of side effects. In no case should an elderly or confused patient be permitted to regulate his own lithium. In these situations, the drug should be dispensed by family members. The physician should emphasize the following points to his patients taking lithium:

1. Lithium carbonate is a salt and is rapidly removed from the body.
2. The patient must take his medication at fixed times if serum determinations are to be accurate.
3. The patient must report missed doses of medication prior to blood sampling.
4. *Under no circumstances should the patient try to "catch up" on missed medication.* (We have seen several patients who have left their lithium at home on weekend trips and have tried to catch up on the missed medication when they returned. Severe lithium toxicity resulted.)
5. A normal diet (including salt) must be maintained and the fluid intake must be at least 2,500 to 3,000 ml. per day, particularly during the initial stabilization period. (Lithium decreases sodium reabsorption by the renal tubules, which may lead to sodium depletion. If hyponatremia occurs, lithium reabsorption is increased and toxicity results.)
6. The patient may experience lithium toxicity if he develops any condition that produces protracted sweating or diarrhea. In such cases, lithium should be temporarily discontinued while supplemental fluid and salt are administered.

TABLE 1.

Signs and Symptoms of Dose-related Lithium Intoxication*

*Initial Response to Therapy***

Fine tremor of hands
Dry mouth
Mildly increased thirst
Mild polyuria
Transient mild nausea

Blood level (mEq. per L.)

1.5:
Increased nausea
Vomiting } Further increases
Diarrhea } lithium toxicity

2.0:
Polyuria
Blurred vision
Muscular weakness
Drowsiness
Dizziness
Vertigo
Increasing confusion
Slurred speech
Transient scotomas
Blackouts
Fasciculations
Increased deep tendon reflexes

2.5:
Myoclonic twitches
Myoclonic movements of entire limb
Choreoathetoid movements
Urinary and fecal incontinence
Increasing restlessness followed by stupor, followed by coma

3.0:
Epileptiform seizure
Cardiac arrhythmias

4.0:
Hypotension
Peripheral vascular collapse

*—*These signs and symptoms may occur in different order or at lower serum levels in susceptible individuals.*

**—*Not toxic signs.*

7. The physician must be contacted immediately if any condition arises which produces fever, such as an infection. If this happens, the daily dose of lithium should be temporarily reduced or the medication should be discontinued.

8. Initial signs of lithium intoxication include diarrhea, vomiting, drowsiness, muscular weakness and loss of coordination. These symptoms usually occur at levels below 2 mEq. per L. At higher levels, giddiness, ataxia, blurred vision, tinnitus and polydipsia occur.

9. The patient should notify his physician immediately if he begins any medication prescribed by another physician. He must also inform any other treating physician that he is taking lithium.

Lithium Toxicity

In general, toxic effects of lithium are related to serum levels. However, several cases of significant toxicity have occurred in patients whose serum levels fell within the "normal therapeutic range." Such cases are rare, but individual variations do occur and clinical judgment, rather than serum levels, must determine management.

Many patients notice the development of gastric discomfort, nausea and fine, rapid tremor of the hand, particularly at the onset of therapy. These symptoms are relatively common and usually abate within one to two weeks. If problematic, they can be reversed by lowering the initial treatment dose. The signs and symptoms of dose-related lithium intoxication are shown in *Table 1*; nondose-related effects are listed in *Table 2*. Some patients with serum lithium in the range of 1.0 to 1.5 mEq. per L., particularly when the concentration has risen rapidly, also experience muscular weakness, urinary frequency, dry mouth and increased thirst, associated with pretibial and hand edema. Such effects usually diminish spontaneously without a reduction in dose; how-

ever, they merit careful monitoring as they may herald a more serious toxicity.

Nausea, vomiting and diarrhea may indicate lithium toxicity or may simply represent "flu symptoms." The patient should be advised to contact his physician immediately should these signs occur. It is prudent to discontinue lithium in these cases until blood levels can be obtained. The pretibial and hand edema is usually not of consequence unless the patient is predisposed to pulmonary emboli. Diuretic therapy is generally ineffective for treating this edema and may produce toxicity. The combination of lithium and diuretics is generally contraindicated. If, for any reason, diuretics must be instituted, careful monitoring of electrolyte balance and renal function is essential.

Early treatment of toxic symptoms is crucial because progression is the rule. Severe symptoms may not appear for three to five days following an overdose, suggesting that delayed absorption may be a critical factor. One patient who attempted suicide by lithium overdose did not become comatose until three days after ingestion.

Enough reports have appeared in the literature to confirm that lithium toxicity may produce asymmetric focal neurologic signs. Although such symptoms are uncommon, the presence of localized neurologic findings does not exclude the possibility of lithium intoxication.

CARDIAC EFFECTS

Effects of lithium on the heart range from benign flattening and inversion of T waves to severe hypotension and cardiovascular collapse, following significant overdose. The use of lithium in patients with preexisting cardiovascular disease should be carefully weighed.

THYROID EFFECTS

Approximately 4 percent of patients receiving lithium develop goiter. The agent acts as a colloid trap and is most likely to produce thyroid changes in individuals with a preexisting low thyroid reserve. Lithium decreases circulating thyroid hormone, which results in increased production of thyroid-stimulating hormone (TSH). The increased TSH production prompts autoregulatory mechanisms which gradually produce a return to chemical baseline. Clinical reports suggest that lithium may cause diffuse, nontender thyroid enlargement, true hypothyroidism or both. The effects are reversed by discontinuing the drug and administering thyroid hormone. Thus, borderline hypothyroidism represents a relative contraindication to the use of lithium.

RENAL EFFECTS

Some patients on lithium therapy develop severe polyuria and polydipsia, as in diabetes insipidus. The syndrome is of renal origin and is not responsive to vasopressin. This nephrogenic diabetes insipidus is reversed by dose reduction or discontinuance of lithium and does not seem to be specifically related to serum lithium levels; *e.g.*, it has occurred at serum levels as low as 0.4 mEq. per L. If lithium must be continued, the syndrome can be paradoxically controlled in

The Author

RICHARD C. W. HALL, M.D.
is associate professor of psychiatry and director of residency training at the University of Texas Medical School at Houston. Dr. Hall was a fellow in psychiatry and behavioral sciences at Johns Hopkins University School of Medicine, Baltimore, where he also completed his psychiatric residency in 1972. He is certified by the American Board of Psychiatry and Neurology and also serves as an examiner for the Board. Dr. Hall has written numerous articles in his field.

TABLE 2.

Nondose-related Side Effects of Lithium

Transient EEG changes: diffuse slowing, widening of frequency spectrum, and potentiation and disorganization of background rhythm
ECG changes: reversible flattening, isoelectricity or inversion of T waves
Headache
Weight gain
Edema of hands and feet
Leukocytosis
Transient hyperglycemia
Albuminuria and glycosuria
Generalized pruritus with or without rash
Cutaneous ulcers
Exacerbation of organic brain syndrome
Diffuse nontoxic goiter with or without hypothyroidism
Nephrogenic diabetes insipidus-like syndrome
Structural damage to nephron with fibrosis

some cases by administration of hydrochlorothiazide or clofibrate (Atromid-S®).

Reports of renal damage occurring in patients on long-term lithium therapy began to appear in 1977. These initial reports described focal nephron atrophy and/or interstitial fibrosis in patients who experienced adverse reactions to lithium, such as frank intoxication, polyuria and polydipsia, or nephrogenic diabetes insipidus. All of these patients had abnormal renal function tests (mainly reduced creatinine clearance and renal concentrating ability) prior to biopsy. In 1978, it was reported that renal damage could be detected at biopsy before any laboratory abnormalities occurred and also that diminished renal function persisted for months after discontinuance of lithium.

Burrows and his associates were able to demonstrate renal changes at biopsy in patients who had taken lithium for only four or five months, and in whom clinical and laboratory tests were normal. They described a unique lesion, consisting of ballooning of cells with vacuolization of the cytoplasm, which was found predominantly in the distal convoluted tubules and collecting ducts. This study suggests that the extent of renal damage is related to the duration of therapy.

A Swedish study showed that renal concentrating capacity is significantly reduced by lithium treatment, decreasing as a direct function of the total lithium dose administered. These decreases were more pronounced when other psychotropic drugs were administered concurrently.

A Danish study of over 150 lithium-treated patients concluded that, in spite of the drug's documented renal effects, the risk of renal insufficiency is remote, particularly if careful attention is paid to maintaining proper fluid and electrolyte balance. Until further studies are reported, these findings should alert the physician to be cautious in prescribing lithium for conditions other than manic-depressive disease of the manic or cyclic type.

Approximately 75 to 80 percent of both sodium and lithium are reabsorbed in the proximal renal tubule. Little or no lithium, however, is reabsorbed in the distal tubule, while a fraction (ranging from almost none to almost all) of the remaining sodium is reabsorbed there, depending on the physiologic state of the individual. The normal individual excretes 20 percent of a filtered lithium load.

Clinical observation has shown that individuals may gradually develop lithium intoxication without evident cause. Polyuria usually occurs during the initial phase of this process, and dilute urine may persist for some time. Urinary output eventually declines, however, and renal failure occurs. Lithium inhibits the effects of aldosterone on the distal nephron, reducing the distal tubule's capacity for sodium reabsorption. Normally, the body compensates for this change by producing more aldosterone. However, in patients

with preexisting subclinical renal impairment, distal sodium reabsorption is unable to compensate for the lithium-induced blockage. Consequently, the proximal sodium reabsorption mechanism is stimulated, causing increased lithium reabsorption. This action increases the serum lithium level, further blocks sodium reabsorption and produces further toxicity.

Factors Predisposing to Lithium Intoxication

The most frequent causes of lithium intoxication are excessive intake, impaired excretion, sodium depletion, changes with pregnancy and individual predisposition.

Excessive Intake. Overdoses of lithium may be deliberate (*e.g.*, when a patient attempts suicide) or accidental (*e.g.*, when an older patient forgets how much medicine he has taken). Overdoses also occur in manic patients who increase their dose in an attempt to control hyperactivity.

Impaired Excretion. Inability to excrete lithium may be a consequence of impaired renal function, which occurs secondary to poor glomerular perfusion or filtration (dehydration, congestive heart failure) or as a result of primary renal disease (glomerular disease or pyelonephritis).

Sodium Depletion. Lithium retention occurs whenever a patient's sodium intake is significantly restricted. In such cases, the body compensates by increasing the percent of filtered sodium reabsorbed at the proximal tubule. Since lithium is also reabsorbed in this situation, gradual toxicity occurs. Lithium retention is also associated with the use of certain diuretics, particularly the thiazides. Toxicity is also likely to occur whenever a mineralocorticoid deficiency exists, *e.g.*, following adrenale tomy.

Changes with Pregnancy. Pregnant women evidence increased clearance of lithium. Consequently, maintenance doses during pregnancy are higher than those recommended for the postpartum period. Thus, toxicity can be expected unless doses are lowered after delivery.

Individual Predisposition. Lithium toxicity occurs more frequently in the very young, in the elderly, in schizophrenics and in patients with organic brain syndromes. Toxicity is also likely to be seen in people with disorders that induce anorexia, nausea and vomiting.

Interaction with Other Drugs

There is considerable controversy and concern regarding lithium's toxic potential when combined with other agents. Cases have been reported which suggest that the combination of lithium and haloperidol (Haldol®) may produce an encephalopathic syndrome, characterized by weakness, fever, lethargy, confusion, tremulousness, extrapyramidal symptoms and irreversible brain damage. Laboratory findings associated with this syndrome include leukocytosis and elevations of BUN, serum enzymes and fasting blood sugar. These reports do not establish a causal relationship. There have been similar reports on the combined use of lithium and thioridazine (Mellaril®). The increased possibility of lithium toxicity when the drug is administered with thiazides is clearly documented. Some reports have also suggested an increased incidence of lithium toxicity when the drug is administered with methyldopa, but this remains unproved.

Treatment of Lithium Intoxication

Once lithium intoxication is suspected, every effort should be made to minimize further absorption of the drug, to maximize its excretion and to provide support. In suicide attempts with lithium, careful screening for the presence of other drugs is indicated. In cases of deliberate or accidental overdose, as much lithium as possible should be removed from the gastrointestinal tract. If the patient is

awake and alert, emesis induced by syrup of ipecac is useful. In an unconscious patient, gastric lavage with a large-bore tube following endotracheal intubation is indicated. As mentioned before, lithium absorption may be delayed and serum levels may rise for several days following acute overdose, since the drug may produce a poorly soluble aggregate in the stomach. Because of the possibility of delayed absorption, lavage is indicated even if the overdose occurred several hours previously. Serum lithium levels and gastric lithium content should be recorded. Activated charcoal is of no use in retarding lithium absorption.

If lithium toxicity is the result of negative sodium balance, caused by either reduced intake or increased excretion of sodium, administration of sodium chloride is indicated. Increasing available sodium is of little value in cases of toxicity secondary to impaired glomerular filtration. However, since these distinctions are often difficult to make in the emergency room, it is suggested that all patients receive from 150 to 300 mEq. of sodium chloride by infusion over a six-hour period, if no specific contraindications are present.

Forced alkaline diuresis, acetazolamide (Diamox®), urea, aminophylline and sodium bicarbonate also increase lithium clearance. Osmotic diuretics, such as mannitol, may also be of assistance. These agents should be considered as adjuncts to the administration of sodium chloride in situations where dialysis is not feasible or available.

In cases of severe intoxication, dialysis is the treatment of choice. Lithium is uniquely suitable to removal by dialysis because of its small molecular size, absence of protein binding and metabolites, and high water solubility. Dialysis should proceed slowly. If serum lithium levels are lowered precipitously, tissue redistribution may cause a rebound resulting in doubling of serum lithium levels. Since the serum lithium reflects cerebral uptake, this situation may worsen central nervous system toxicity.

Although dialysis is extremely useful, one should not labor under the misconception that it will guarantee a successful outcome. Several cases have been reported where severe neurologic damage or death followed lithium overdose despite early dialysis. It must be remembered that toxicity depends on both the absolute magnitude and the duration of serum elevation. In our opinion, dialysis is indicated when serum lithium levels exceed 4 mEq. per L., regardless of the appearance of the patient, and when the serum lithium concentration is between 2 and 4 mEq. per L. and the patient appears significantly intoxicated.

Following an acute overdose, regardless of the patient's condition, a period of careful in-hospital observation is indicated, because clinical deterioration may not occur for hours or even days after poisoning. Recovery from lithium poisoning occurs slowly over a period of approximately one week. Neurologic improvement may lag considerably behind the return of serum lithium to therapeutic levels. A case has been reported in which a patient with lithium overdose showed no neurologic abnormalities until 45 hours after hospital admission. ■

SUGGESTED READING

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