Clinical Manifestations and Management of Acute Lithium Intoxication
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Acute lithium intoxication is a frequent complication of chronic lithium therapy for manic depressive disorders. Because of lithium's narrow therapeutic index and widespread use, lithium intoxication remains prevalent in 1994. This review summarizes information on the renal handling of lithium and the physiologic basis for toxicity. Recent reports that describe previously unrecognized side effects of lithium intoxication are discussed. We also present management guidelines based upon our understanding of the renal handling of lithium. In this review we compare the effectiveness of lithium removal by various dialysis methods, including bicarbonate dialysis, peritoneal dialysis and continuous arteriovenous hemofiltration. Hemodialysis remains the cornerstone for the treatment of acute lithium toxicity.

Lithium is effective in controlling manic excitement and preventing recurring manic depressive episodes. Its use brings symptomatic improvement in 70% to 80% of patients with these disorders. It has become indispensable in psychiatry, allowing rehabilitation of many patients who would otherwise require long-term hospitalization.

Nevertheless, numerous cases of lithium intoxication have been noted since Cade introduced lithium for the management of mania in 1949. Because of the drug's frequent use and narrow therapeutic index, lithium intoxication continues to be prevalent. Hansen and Amdisen reported 23 cases of lithium intoxication and reviewed 100 other cases in the literature. Since their comprehensive review, case reports have continued to appear, some characterizing previously unrecognized side effects and long-term sequelae of lithium intoxication. Furthermore, the kinetics of lithium handling by various therapeutic modalities during lithium intoxication have been characterized better, thus making rational medical management possible.

This review describes (1) conditions predisposing to lithium intoxication or associated with it; (2) clinical manifestations of lithium intoxication, particularly previously unrecognized side effects; and (3) management options, emphasizing the kinetics of lithium removal by various therapeutic modalities.

PHARMACOLOGY
Lithium, along with sodium, potassium, rubidium, and cesium, is a Group IA alkali metal. Lithium's structure is similar to sodium and potassium, and it accordingly shares characteristics with them. However, lithium's smaller radius (0.60 Å) when compared to sodium (0.95 Å) and potassium (1.33 Å) has ramifications for its relative effectiveness in various cellular processes. For example, unlike sodium and potassium, only a small gradient for lithium can be maintained across biologic membranes.

Lithium is usually administered as lithium carbonate, with 300 mg of the compound containing 8.12 mEq of lithium ion. Following oral administration, lithium is absorbed completely after approximately 8 hours, with peak levels occurring at 2 to 4 hours. Serum levels are measured by flame photometry and atomic absorption spectrophotometry. The therapeutic range varies from one laboratory to the next. In our institution it is 0.7 to 1.2 mEq/L. Lithium is not protein bound. It distributes freely in total body water everywhere but in the cerebrospinal fluid, and accumulates in various tissues. The volume of distribution is approximately 0.7 to 0.9 L/kg. Lithium concentration in cerebrospinal fluid is 40% of plasma levels as a result of transport of lithium out of the cerebrospinal fluid by brain capillary endothelium and/or arachnoid membrane.

The plasma elimination half-life of a single dose of lithium is between 12 and 27 hours. It varies with age, from 18 to 20 hours in young adults to approximately 30 hours in elderly patients. Most recently it has been suggested that elimination half-life varies with duration of therapy. Goodnick et al. discontinued lithium in 30 hospitalized patients who had been taking stable doses of the drug, then determined the plasma lithium elimination half-life. For patients without prior lithium therapy, those with 1 year of therapy, and those with greater than 1 year of therapy, the half-life was 29, 40, and 58 hours, respectively. Thus, in patients treated chronically with lithium, the elimination half-life may be considerably longer than reported previously. Intracellular accu-
imulation and inhibition of lithium efflux following chronic lithium therapy likely prolongs the elimination half-life. Lithium is known to be concentrated variably in liver, bone, muscle, brain, kidney, and thyroid. Moreover, the lithium efflux from red blood cells is inhibited following chronic therapy.

RENOAL HANDLING OF LITHIUM

Approximately 95% of a single dose of lithium is excreted by the kidney with trace amounts found in feces. Lithium is not bound to proteins and is therefore freely filtered by the glomerulus. Eighty percent of the filtered load of lithium is reabsorbed and 20% excreted in the urine. Renal lithium clearance in normal individuals is 10 to 40 mL/min. The fractional lithium clearance is estimated to be 0.17 to 0.29.

Because lithium clearance is proportional to glomerular filtration rate, factors affecting the glomerular filtration rate have a significant influence on the clearance of lithium. Thus substantial reductions in lithium dosage must be made in patients with chronic renal insufficiency. Furthermore, alterations in the proximal reabsorption of lithium may alter the fractional excretion of lithium without significantly affecting glomerular filtration. This has important therapeutic implications, since drugs known to inhibit proximal reabsorption of lithium may increase fractional excretion of lithium and thus speed up lithium removal.

Clearance studies with diuretics suggest that the primary site of lithium is the proximal tubule. Diuretics that alter proximal reabsorption of sodium, such as acetazolamide or other diuretics with carbonic anhydrase inhibiting properties, aminophylline, and urea increase fractional excretion of lithium. Diuretics that act distal to the proximal tubule, such as thiazides, ethacrynic acid, and spironolactone have no effect on fractional excretion of lithium. Physiologic studies indicate that most of the filtered load of lithium is reabsorbed by the proximal tubule and a fraction is reabsorbed by the loop of Henle and distal tubule segments. Microperuncture studies by Hayslett and Kashgarian indicate that 57% of the filtered load of lithium is reabsorbed by the proximal tubule and another 18% is reabsorbed by the segment between the late proximal tubule and early distal tubule.

Forrest et al determined that lithium concentrations increased from cortex to papilla, suggesting that the loop of Henle reabsorbs the drug. A disproportionate increase in lithium clearance has been observed during mineralocorticoid escape, suggesting inhibition of lithium reabsorption by the loop of Henle as well as the proximal tubule. Furthermore, under conditions of low sodium excretion reabsorption may occur in the distal nephron. Inhibition of lithium reabsorption by bumetanide and amiloride suggests that the thick ascending limb and collecting duct also reabsorb lithium.

RISK FACTORS FOR INTOXICATION

Patients with lithium intoxication may present with a variety of clinical manifestations. The severity of symptoms is generally proportional to the degree of elevation of serum lithium levels. It has become increasingly evident, however, that symptoms do not necessarily correlate with lithium levels. Symptoms of toxicity have occurred at therapeutic levels and minimal symptoms have resulted from high levels.

As a rule, however, serum lithium levels of 1.5 to 2.5 mEq/L 12 hours after the last dose of lithium are usually accompanied by slight or moderate symptoms of intoxication, values of 2.5 to 3.5 mEq/L are serious, and values above 3.5 mEq/L are life threatening. The patient's history often reveals conditions predisposing to lithium intoxication (Table I). These include advanced age, schizophrenia, pre-existing brain damage, and rapid rise in lithium serum levels following administration. Other conditions such as diarrhea, vomiting, inadequate fluid therapy following surgery, diuretics and volume depletion predispose to lithium toxicity because of their association with sodium depletion. Because sodium promotes lithium clearance, a decrease in dietary sodium intake or chronic therapy with furosemide or thiazide can increase risk of intoxication.

Lithium intoxication has also been reported with the use of the nonsteroidal anti-inflammatory drug (NSAID) piroxicam. Studies in humans have shown that both indomethacin and diclofenac, two classes of NSAIDs, raise plasma lithium levels and decrease lithium clearance. A number of other NSAIDs have been shown to increase lithium levels in normal volunteers and patients chronically treated with lithium. The effect is variable, and an increase
of approximately 60% has been observed. Indomethacin appears to have the greatest effect on lithium levels, while sulindac and aspirin seem not to alter them.

The mechanism by which NSAIDs inhibit lithium clearance is not known. Some evidence points toward an indirect effect through alteration of the sodium balance. Prostaglandin dependent sodium excretion has been shown to affect various segments of the nephron including the thick and thin ascending limb of the loop of Henle and the medullary collecting duct, but not the proximal tubule. Moreover, in isolated perfused rabbit tubules, the inhibitory effects of prostaglandin inhibition on sodium reabsorption have been demonstrated. Prostaglandins inhibit sodium reabsorption in the cortical collecting tubules, outer medullary collecting tubules, and medullary thick ascending limb of Henle.

In patients with normal renal function, it is unlikely that alteration in lithium clearance is due to a reduction of glomerular filtration, because NSAIDs do not change glomerular filtration in individuals with normal renal function. Patients with congestive heart failure and volume depletion, however, require prostaglandins to maintain their renal blood flow and glomerular filtration rate. In this group, prostaglandin inhibition by NSAIDs can severely reduce glomerular filtration and lithium clearance and thereby increase the risk of lithium toxicity.

The last several years have produced case reports of acute lithium intoxication with the use of the angiotensin converting enzyme (ACE) inhibitors. Without any change in lithium dosage, elevated lithium levels developed 3 to 4 weeks after starting ACE inhibitors. The mechanism appears to be as follows. During states of volume depletion and decreased renal blood flow, the glomerular filtration rate is maintained by the action of angiotension II on increasing efferent arteriolar constriction. ACE inhibitors block this compensatory action, decreasing glomerular filtration and fractional excretion of lithium. The use of ACE inhibitors can result in a predisposition to lithium toxicity. In normal individuals, ACE inhibitors increase glomerular filtration, sodium excretion, and fractional excretion of lithium in normal individuals.

In summary, the use of an NSAID or an ACE inhibitor increases susceptibility to lithium toxicity only in certain clinical conditions—most importantly congestive heart failure or volume depletion. In this context, it is important to note that long-term lithium therapy can cause nephrogenic diabetes insipidus and polyuria.

### TABLE II

<table>
<thead>
<tr>
<th>Clinical Manifestations of Lithium Intoxication</th>
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<tbody>
<tr>
<td>Central nervous system</td>
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<tr>
<td>Altered state of consciousness (confusion to coma)</td>
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<tr>
<td>Cerebellar symptoms</td>
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<tr>
<td>Dysarthria</td>
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<td>Ataxia</td>
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<td>Nystagmus</td>
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<td>Tremors</td>
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<td>Basal ganglia</td>
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<td>Choreiform movements</td>
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<td>Parkinsonian movements</td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Death</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Nausea/vomiting</td>
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<tr>
<td>Bloating</td>
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<tr>
<td>Cardiac</td>
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<tr>
<td>Syncope</td>
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<tr>
<td>Renal</td>
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<tr>
<td>Polyuria</td>
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<tr>
<td>Polydipsia</td>
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<tr>
<td>Renal insufficiency</td>
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<tr>
<td>Neuromuscular</td>
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<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Myopathy</td>
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<tr>
<td>Endocrine</td>
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<tr>
<td>Hypothermia</td>
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<tr>
<td>Hyperthermia</td>
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Although patients with lithium intoxication may present with a variety of clinical manifestations, as listed in Table II, neurologic symptoms appear to dominate. These are well described in numerous case reports. They often develop gradually with initial confusion, impaired consciousness leading to coma, and occasionally death. Cerebellar manifestations are often prominent, including dysarthria, truncal ataxia, broad-based ataxic gait, nystagmus, and varying degrees of incoordination. Lithium intoxication can also induce seizures and involve the basal ganglia to cause choreiform and parkinsonian movements.

Although lithium therapy often produces gastric irritation, epigastric bloating, abdominal pain, nausea, vomiting and diarrhea, these are not severe manifestations.

Electrocardiographic changes are frequently associated with lithium therapy. Transient ST segment depression and/or inverted T-waves in V4-6 have been described in patients with lithium intoxication. Few case reports have described cardiac symptoms as manifestations of lithium intoxication. Some patients have developed sinus node dysfunction leading to syncope.

Polyuria and polydipsia are frequent side effects of lithium therapy, with an estimated prevalence of 20% to 70%. The concentrating defect may develop in patients with therapeutic serum levels of the drug, as well as in those who are overtly toxic. This is important pathogenically as polyuria may lead to volume depletion and decrease in fractional excretion of lithium.
Lithium. Mechanisms by which lithium produces polyuria are summarized by Singer. They include primary polydipsia, central diabetes insipidus, and nephrogenic diabetes insipidus.

Other less common manifestations of lithium intoxication are hyperthermia, hypothermia, peripheral neuropathy, myopathy, and severe leukopenia.

**MANAGEMENT**

The initial management of patients with lithium intoxication is determined by the degree of intoxication. As noted in Table II, patients present with a variety of clinical manifestations resulting from chronic lithium therapy or acute overdosage.

Patients who appear to have severe impairment of consciousness should have their oral airway protected. Gastric lavage should be performed in acute overdosage. Activated charcoal is useless as a gastrointestinal decontaminant in lithium overdose because it does not absorb strongly ionized chemicals. Polyethylene glycol (Colyte, Reed & Carnrick, Jersey City, New Jersey; GoLytely, Braintree Laboratories, Braintree, Massachusetts) has been shown to be effective. In a controlled study with 10 normal subjects, whole bowel irrigation with polyethylene glycol administered via a nasogastric tube was started 1 hour after ingestion 0.80 mEq/kg of sustained release lithium. Ten liters of polyethylene glycol was given over 5 hours. The mean serum lithium concentration was significantly decreased within 1 hour of beginning irrigation. Whole bowel irrigation is recommended as the decontaminant procedure of choice in acute ingestion of sustained release lithium.

Fluid resuscitation is critical in the initial management of lithium intoxication. Drug-induced urinary concentrating defects can significantly deplete volume. Many patients have volume responsive decreases in renal function. The administration of large amounts of isotonic saline requires careful monitoring to avoid the danger of severe hypernatremia. Lithium removal is the final step after fluid resuscitation. Various modalities for lithium removal are listed in Table III. The efficacy of each modality can be assessed by comparing lithium clearances. Because there are no controlled studies measuring lithium clearance during intoxication, the following data on lithium clearance rely heavily on case reports.

In normal individuals, renal lithium clearance has been reported to be 10 to 40 mL/min. In patients with lithium intoxication, Hansen and Amdisen found clearance rates of 0.9 to 18.4 mL/min. Of their 23 patients, only 5 had normal renal function, defined as creatinine clearance greater than 78 mL/min. In sum, patients with lithium intoxication have scant ability to remove lithium through renal excretion.

Because 80% of lithium is reabsorbed in the proximal tubule, factors that decrease proximal lithium reabsorption may enhance removal of the drug during states of intoxication. Since sodium balance alters the clearance of lithium, forced diuresis with isotonic saline has been attempted as treatment of lithium intoxication. O'Connor and Gleeson reported renal lithium clearance in a patient with lithium intoxication to be 39 mL/min when urine output was maintained at 500 mL/h. Hansen and Amdisen had poor success with forced diuresis. Fractional lithium clearance increased in 2 of their 7 patients, but decreased in the other 5. Lithium excretion averaged 29.2 mmol/d before sodium chloride infusion and 26.5 mmol/d during infusion. Forced diuresis is not recommended for severe lithium intoxication because consistent therapeutic benefits have not been achieved and because of the potential complication of hypernatremia. However in those patients with impaired lithium clearance as a result of volume contraction, isotonic saline may transiently increase lithium clearance.

The effects of various agents on lithium clearance after a single dose of the drug have been studied in humans. Water loading, furosemide, thiazide, ethacrynic acid, ammonium chloride, and spironolactone did not increase clearance of lithium. Sodium bicarbonate, acetazolamide, urea, and aminophylline have been effective. Clinical studies employing these agents for lithium removal during intoxication have not been reported.

Peritoneal dialysis is another means of removing lithium. Wilson et al attained clearances of 13 to 15 mL/min with exchanges of 2L/h. O'Connor and Gleeson achieved similar results, reporting lithium clearances of 9 mL/min with frequent 2L exchanges. Although lithium removal via peritoneal dialysis is no more efficient than forced diuresis, it is easier, avoids large volumes of isotonic saline, and removes lithium continuously over a prolonged period of time.

Hemodialysis remains the mainstay of therapy in severe lithium intoxication. With its small atomic weight and negligible protein binding, lithium is one of the most readily dialyzable toxins. Hansen and Amdisen reported clearances of 8 patients undergo-

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**TABLE III**

<table>
<thead>
<tr>
<th>Mode</th>
<th>Lithium Clearance (mL/min)</th>
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<tr>
<td>Renal excretion</td>
<td>10-40</td>
</tr>
<tr>
<td>Forced diuresis</td>
<td>0.9-39</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>6-10</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>70-170</td>
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</table>

*Blood flow = 126-250 mL/min.*
ing hemodialysis for lithium intoxication. With mean blood flows of 126 mL/min and dialysate flows of 600 mL/min, lithium clearance was 94 mL/min. Cledeninn\textsuperscript{94} investigated the pharmacokinetics of lithium removal in a patient with an acute overdose. With blood flows of 150 mL/min, the average whole blood lithium clearance was approximately 70 mL/min. Fenves et al\textsuperscript{95} reported lithium clearance via hemodialysis in a patient with lithium intoxication to be approximately 170 mL/min while using blood flows of 200 to 250 mL/min. Since lithium clearance is nearly proportional to blood flow, elevated blood flows of 300 mL/min can further enhance clearance. Table III clearly demonstrates the superiority of hemodialysis to other methods.

The duration of hemodialysis should be guided by serial serum lithium levels. Dialysis may be terminated when these levels approach the therapeutic range. It is important to bear in mind that serum levels may rebound up following hemodialysis and require repeat dialysis.\textsuperscript{5,96,97} This effect occurs as a result of continued absorption of lithium from the gastrointestinal tract as well as redistribution of lithium from intracellular stores. The extraction of lithium from intracellular stores as reflected in red blood cell clearance is much slower than extraction from the serum, at only 10 to 13 mL/min.\textsuperscript{94} This contributes to the rebound effect.

The rebound increase in serum lithium levels that follows conventional hemodialysis increase may be partly due to the choice of alkali used in the dialysate. In one study, 98% of the lithium that was removed by acetate dialysis was estimated to come from the extracellular compartment.\textsuperscript{96} In contrast, with bicarbonate dialysis, 40% of the lithium removed was derived from the extracellular compartment and 60% from the intracellular compartment. Based on this observation and experimental studies showing that organic anions induce cell accumulation of lithium,\textsuperscript{97} Szerlip et al\textsuperscript{96} hypothesized that acetate diffuses into cells as acetic acid and the protein which is liberated within the cell is exchanged for lithium via the \text{Na(Li)/H} antiporter.

An alternative to conventional hemodialysis when appropriate facilities are not readily available is continuous arteriovenous hemodiafiltration.\textsuperscript{98} This modality achieved a lithium clearance of 20.5 mL/min. It is suggested that this technique requires about 24 hours of treatment for optimal results.

Table IV summarizes our approach to managing patients with lithium intoxication. Initially the degree of consciousness and volume status should be assessed. The oral airway should be protected, and if necessary isotonic saline should be administered for volume repletion. Following these critical maneuvers, the focus should move to lithium removal. The method of lithium removal for achieving clearance depends on the serum lithium levels, severity of symptoms, and duration of intoxication.

Although each patient should be evaluated individually, rough guidelines for rational therapeutic options can be derived from a knowledge of the pharmacokinetics of lithium removal. For patients with minimal symptoms, normal renal function, and serum lithium levels of less than 2.5 mEq/L, intravenous hydration may be adequate. Urinary electrolytes should be evaluated to guide the choice of replacement fluid so as to avoid hypernatremia. For severe lithium intoxication, hemodialysis is clearly superior to other modalities. Peritoneal dialysis or continuous arteriovenous hemofiltration may be used if hemodialysis is not available.

**OUTCOME**

Most patients treated for lithium intoxication have favorable outcomes with reversal of neurologic deficits.\textsuperscript{5} Some recent reports, however, have described long lasting neurologic sequelae.\textsuperscript{101-104} Shon\textsuperscript{105} concluded that permanent neurologic changes appear to stem primarily from cerebellar deficits. Prominent manifestations include ataxic scanning articulation, gait and truncal ataxia, inability to perform heel-to-shin and finger-to-nose maneuvers, bilateral adiadochokinesia, nystagmus, hypertonic musculature, short-term memory deficits, and dementia. Concomitant therapy with neuroleptics, associated multi-system organ failure, and alcohol abuse have clouded the interpretation of the literature. Overall, it seems likely that lithium intoxication may lead to long-term neurologic sequelae.

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