Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose

FOURTH EDITION

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30 *Lithium*

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At a Glance...

- Lithium is a drug with a narrow therapeutic index.
- It has a two-compartment volume of distribution moving from extracellular to intracellular compartments.
- Lithium is eliminated almost entirely by the kidneys.
- Its toxicity is most commonly manifested by CNS symptoms.
- Acute lithium overdose differs significantly from chronic lithium intoxication.
- Serum levels do not correlate with systemic toxicity.
- Hemodialysis is an ideal treatment modality but should be reserved for patients exhibiting signs of severe intoxication and should be based on clinical and kinetic criteria.

INTRODUCTION

Lithium was discovered in 1818 and initially used for the treatment of gout, rheumatism, and renal calculi.[1,2] In the early 1900s it was used as a salt substitute but was later abandoned because of toxic effects. It was also once present in the soft drink 7-Up.[3] Although Aulde and Lange recognized in the 1880s that lithium could be used to treat depression, it was not until the 1950s that Cade and Schou established its use as a treatment for bipolar disorder.[4] In 1970, the U.S. Food and Drug Administration (FDA) approved its use for the treatment of acute mania. Currently, lithium is used to treat a wide variety of disorders (Box 30-1) from bipolar affective disorder and alcoholism to prophylaxis for cluster headache. It remains the drug of choice for the treatment of recurrent bipolar illness.[5]

With increasing use of lithium comes an increased risk for toxic effects. It is estimated that up to 90% of patients taking lithium have at some time experienced signs and symptoms of toxicity.[6] In 1991, the American Association of Poison Control Centers reported 4149 cases of lithium exposure, with 622 (15%) resulting in moderate to severe intoxication and 12 in death.[7] In 2002, 4954 cases were reported (one third being unintentional exposures) with 1527 resulting in moderate to severe intoxication and 15 in death. Although death is rare, the risks for morbidity and prolonged hospitalization emphasize the importance of appropriate management.

BOX 30-1 THERAPEUTIC USES OF LITHIUM

Psychiatric Disorders	Nonpsychiatric Disorders
Manic-depressive (bipolar) illness*	? Pain
Unipolar depressive illness	Graves' disease
Behavior disorders	? Premenstrual tension
Character disorders	? Leukopenia/chemotherapy
Pain	? Felty's syndrome
Alcoholism/drug abuse	? Thyrotoxicosis
Premenstrual tension	? Tardive dyskinesia
Organic brain syndrome	? Huntington's chorea
Cycloid psychosis	? Pancreatic cholera syndrome
Anorexia nervosa	? Syndrome of inappropriate antidiuretic hormone secretion
Schizoaffective disorders	
Steroid-induced psychosis	

*Only approved use for lithium in the United States; other uses are experimental.

PHARMACOLOGY

Lithium is the lightest alkali metal and has no known physiologic role. Its mechanism of action is not clearly understood. It inhibits the release of norepinephrine and augments its reuptake.[8] It also depletes brain inositol, which is a precursor in the phosphatidylinositol pathway assisting in signal transduction of hormones and neurotransmitters.[1] This effect may result in reduced responsiveness to α-adrenergic stimulation.[9] Other proposed mechanisms include inhibition of G proteins crucial to ion channel opening,[10] stimulation of release of serotonin from the hippocampus, and inhibition of adenylate cyclase.[8] These inhibitory effects may decrease neuronal responsiveness to neurotransmitters. Additionally, because lithium is a cation, it behaves similarly to potassium and sodium, thereby affecting ion transport and cell membrane potential.

PHARMACOKINETICS

Lithium is dispensed in a variety of formulations (Table 30-1) some of which are sustained-release preparations. Lithium is rapidly absorbed, reaching peak levels in 1 to 3 hours in regular preparations and 4 to 12 hours in sustained-release preparations. The bioavailability for most preparations is nearly 100%. It is neither protein bound nor metabolized. Lithium initially has a volume of distribution approximately 0.4 L/kg. However, as the ion moves from extracellular compartments to intracellular compartments over 6 to 8 hours, the final volume of distribution is between 0.6 and 0.9 L/kg.[11] This process, which takes up to 6 to 10 days to reach final equilibrium, reflects the amount of time required to achieve therapeutic response. Serum lithium levels measure only the extracellular concentration of lithium. Yet, lithium exerts its effects once it has moved to its intracellular

TABLE 30-1 Some Available Lithium (Li) Preparations*

TRADE NAME	CHEMICAL FORMULATION	DOSE FORMS
United States		
Lithane (Miles Pharmaceutical)	Lithium carbonate	Tablets, 300 mg
Lithium carbonate USP	Lithium carbonate	Capsules, 150 mg, 300 mg, 600 mg; tablets, 300 mg
Lithium citrate syrup USP (Roxane)	Lithium citrate	Syrup, 8 mEq/5 mL—equivalent to 300 mg of lithium carbonate
Cibalith-S (CIBA)	Lithium citrate	Syrup, 8 mEq/5 mL—equivalent to 300 mg of lithium carbonate
Lithobid (CIBA)	Lithium carbonate	Tablets, 300 mg (sustained release)
Eskalith (SmithKline)	Lithium carbonate	Capsules and tablets, 300 mg
Eskalith CR (SmithKline)	Lithium carbonate	Tablets, 300 mg, 450 mg; capsules, 300 mg (sustained release)
Canada		
Carbolith (ICN)	Lithium carbonate	Capsules and tablets, 300 mg
Lithane (Pfizer)	Lithium carbonate	As above
Lithizine (Maney)	Lithium carbonate	As above
United Kingdom	Lithium carbonate	400 mg tablets also available
Scandinavia		
Litarex	Lithium carbonate	Sustained-release formulation

*Molecular mass = 73.89 daltons; atomic number, 3; atomic weight, 6.94; emission line on flame photometer, 671 nm.

compartment. This two-compartment phenomenon explains why patients can be initially asymptomatic in the setting of significantly elevated serum levels.

Lithium has a predilection for accumulation in liver, bone, muscle, brain, kidney, and thyroid.[12] The highest levels are found in the brain and kidney,[11] and toxicity is most commonly associated with these organs.

Ninety-five percent of lithium is excreted by the kidneys, while the remainder is eliminated via sweat and feces. Lithium is handled similarly to sodium by the kidney, and approximately 75% of the filtered load is reabsorbed in the proximal tubule.[13] The renal clearance is between 10 mL and 40 mL/min.[14] Sodium depletion can increase lithium reabsorption significantly. Consequently, volume depletion from diuretics, dehydration, febrile illness, or gastrointestinal (GI) loss can lead to elevated lithium levels in the serum.

The serum elimination half-life of lithium can vary from 12 to 27 hours. In patients with chronic intoxication the half-life can be prolonged up to 48 hours.[15] The half-life of lithium may vary significantly with duration of therapy.[16] It has been hypothesized that this phenomenon may be due in part to inhibition of lithium efflux from cells by the drug itself during chronic therapy.

The usual renal clearance of lithium is 10 to 40 mL/min. In the elderly, renal clearance may be reduced to 15 mL/min and the elimination half-life can be as long as 58 hours. There is also a propensity toward a smaller final volume of distribution in the elderly.[17] In a study of hospitalized patients with lithium toxicity, age greater than 65 years was associated with a significantly higher likelihood of toxic lithium level.[18]

During the third trimester of pregnancy, lithium clearance will usually increase, thereby creating difficulties with serum monitoring.[17] Lithium freely crosses the placenta and is also excreted in breast milk.[19] It is labeled as pregnancy class D and has been implicated in causing an increased risk of congenital cardiac defects, particularly Ebstein's anomaly. Breast-feeding infants of mothers taking lithium have been reported to have signs of cyanosis, hypotonia, and lethargy.[20]

Multiple medication interactions are associated with lithium (Table 30-2). It has been reported to cause neuroleptic malignant syndrome in combination therapy with neuroleptic agents or by itself in overdose. Additionally, diuretics that deplete sodium and water will indirectly result in lithium toxicity by enhancing its reabsorption in the proximal tubules. Most notable, however, are the drug interactions that affect lithium clearance. Studies in both healthy patients given lithium and those receiving chronic lithium therapy have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease lithium clearance and raise plasma lithium levels.[23] This may be secondary to prostaglandin inhibition causing a reduction in glomerular filtration rate (GFR) and subsequent sodium (and lithium) reabsorption in patients with preexisting volume depletion. Angiotensin-converting enzyme (ACE) inhibitors also contribute to lithium toxicity in volume-depleted patients by causing a further decrease in GFR.

TOXICOLOGY

Lithium toxicity can be classified into three major categories. It may occur as the result of an *acute* overdose (in a lithium-naive patient), acute overdose in a patient on chronic therapy (*acute-on-chronic*), or *chronic* overmedication or drug accumulation. Generally, chronic intoxication is associated with the most serious toxicity.

Accumulation of lithium may result from excessive intake or impaired excretion. Excessive intake is seen in the acute and acute-on-chronic overdose settings in which a patient intentionally ingests an excessive amount

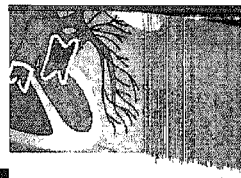


TABLE 30-2 Known Drug Interactions with Lithium

DRUG	EFFECTS OF INTERACTION
Haloperidol	Rigidity, ataxia, oral tardive dyskinesia, ↑ depression, ↑ haloperidol toxicity
Tricyclic antidepressants (TCAs)	Additive antidepressant effect, hypotension, delirium, seizures, increase in blood pressure if hypotension secondary to TCA
Phenothiazines	↑ Lithium and phenothiazine toxicity, ↑ depression along with toxicity
Benzodiazepines	↑ Depression
Neuromuscular blockers	↑ Neuromuscular blockade
Methyldopa	↑ Parkinsonian syndrome
Nonsteroidal anti-inflammatory drugs: indomethacin, piroxicam, mefenamic acid, phenylbutazone	Partial reversal of nephrogenic diabetes insipidus and ↑ serum lithium, ↓ renal lithium clearance
Phenytoin	Polyuria, polydipsia, tremor
Calcium channel blockers: verapamil, nifedipine, diltiazem	Additive or synergistic action with lithium
Angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril)	Reduced glomerular filtration rate, ↓ lithium clearance
Diuretics	
Thiazides	↑ Serum lithium
Osmotics, acetazolamide, sodium bicarbonate	↑ Urinary lithium excretion
Furosemide	No change in serum lithium, unless induces significant sodium loss
Potassium-sparing diuretics and potassium supplements	Abolish distal renal tubular acidosis and may prevent renal lithium toxicity

of lithium tablets in a suicidal or accidental ingestion. Excessive intake also occurs when dose modifications are made for the patient chronically taking lithium.

Impaired excretion of lithium occurs from a variety of factors. Any condition in which sodium and volume depletion occurs may lead to increased reabsorption of the drug in the kidneys. Vomiting, diarrhea, febrile illness, renal insufficiency, excessive exercise, water restriction, excessive sweating, low sodium diet, and congestive heart failure all can increase the risk for lithium toxicity. Concomitant administration of drugs that decrease GFR will also contribute to chronic toxicity. Other factors that play a role in toxicity include duration of therapy[16] and individual tolerance to lithium.[2]

Patients on chronic lithium therapy may develop nephrogenic diabetes insipidus (NDI), which can trigger a cascade of symptoms and signs of lithium toxicity. However, most patients will develop symptoms of polyuria without full-blown NDI. Up to 37% of patients taking therapeutic doses of lithium experience symptoms of polyuria.[24] This is attributable to impaired urinary concentrating ability by the kidneys. This effect coupled with any intercurrent illness can trigger the vicious cycle of lithium toxicity (Fig. 30-1). With sodium and volume depletion, the excretion and clearance of lithium decreases as the kidney increases its reabsorption of the cation. The increased reabsorption leads to elevated levels of serum lithium, which in turn continues to adversely affect the kidneys' ability to concentrate urine. Consequently, patients on chronic lithium therapy who exhibit symptoms of polyuria (or NDI) are at increased risk for developing lithium toxicity.[6]

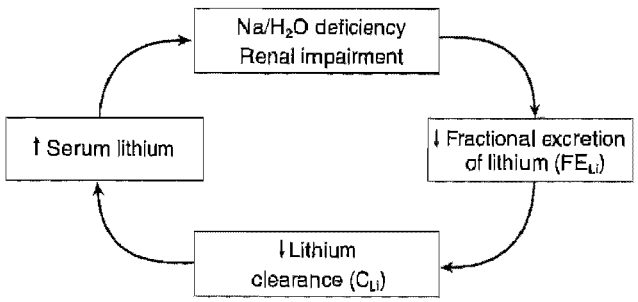


FIGURE 30-1 The vicious cycle of sodium and water depletion and lithium toxicity.

CLINICAL MANIFESTATIONS

The clinical manifestations of lithium toxicity are primarily related to the central nervous system (CNS) and kidneys. In addition, gastrointestinal, cardiovascular, and endocrine side effects are commonly reported.

Neurologic symptoms of intoxication include coarse tremor, dysarthria, ataxia, nystagmus, slurred speech, hyperreflexia, and myoclonia. Patients often have alterations in level of consciousness ranging from mild confusion to delirium, agitation, seizures, and coma. Some patients on chronic therapy complain of prodromal symptoms of nervousness prior to more objective signs of intoxication.[8] Although most patients recover after lithium intoxication, there are reports of neurologic sequelae including scanning speech, ataxia, memory deficits, and choreoathetoid movements persisting for 12 months or even permanently.[25-28]

Renal toxicity is more common in patients on chronic lithium therapy. Toxicity includes impaired urinary concentrating ability, NDI, and sodium-losing nephritis. Previous studies have suggested the incidence of polyuria to be as high as 37% and worsened by concomitant use of serotoninergic antidepressants.[24] Nephrotic syndrome, acute tubular necrosis, and chronic interstitial nephropathy have also been described in association with lithium therapy.

Lithium is the most common cause of drug-induced NDI.[29] The mechanism is not entirely understood. Lithium enters the renal tubules via sodium channels and modulates the function of certain G proteins, thereby lowering the levels of cyclic adenosine monophosphate (cAMP). The lowered intracellular cAMP may contribute to a decrease in transcription and expression of the antidiuretic hormone–sensitive aquaporin-2 water channels[30] responsible for water reabsorption in the kidney. NDI is characterized by polyuria, polydipsia, hypernatremia, and low urine osmolality. Elevated serum osmolality is also expected, but most patients are able to compensate by excessive fluid intake on a daily basis. NDI can significantly predispose patients to lithium toxicity via volume depletion, lithium reabsorption, and the vicious cycle of renal toxicity. Treatment of lithium-induced NDI includes discontinuation of the drug and administration of amiloride,[31] NSAIDS, or thiazide diuretics.[32-34] Cases of persistent NDI after discontinuation of lithium for up to 57 months have been described.[35]

Cardiovascular effects are usually mild and nonspecific. Patients may experience mild hypertension, bradycardia, or tachycardia. Electrocardiographic changes can include transient ST depression, flattened or inverted T waves, QRS widening, QT prolongation, or intraventricular conduction delays. Nearly all patients taking lithium will develop T wave flattening. Sinus node dysfunction is the most commonly reported conduction defect followed by QT prolongation, intraventricular conduction defects, and U waves. Although these findings are reversible, their prevalence and significance are undetermined.[36] In rare circumstances, severe ventricular arrhythmias and myocardial infarction have been described in acute overdoses.[37]

Gastrointestinal symptoms are also more common in the acute overdose setting. Symptoms include nausea, vomiting, diarrhea, anorexia, and bloating and typically occur within 1 hour of ingestion.

Endocrine effects from lithium toxicity most commonly include hypothyroidism via inhibition of thyroid hormone synthesis and subsequent release (in 3% to 60% of patients taking lithium).[38] Less commonly seen is hyperthyroidism, which may not only mask symptoms of lithium toxicity but can increase toxicity by inducing cellular unresponsiveness and altered renal tubular handling of lithium.[38] Lithium is also associated with hyperparathyroidism, hypothermia, and less frequently hyperthermia.

DIAGNOSIS

Degree of intoxication is important for understanding the diagnosis and management of lithium toxicity. Severity of lithium toxicity is most frequently arbitrarily divided into three grades: mild, moderate, and severe[5] (Table 30-3). This grading system was first described by Hansen and Amdisen in 1978[4] and has been used with some degree of consistency throughout the literature. *Mild* symptoms include nausea, vomiting, lethargy, tremor, and fatigue. Symptoms of *moderate* intoxication are confusion, agitation, delirium, tachycardia, and hypertonia. Coma, seizures, hyperthermia, and hypotension characterize *severe* intoxication.

Patient History

Diagnosis and classification (acute, acute-on-chronic, or chronic) of lithium intoxication can be difficult. The prevalence of neurologic symptoms should alert the clinician to the possibility of lithium poisoning. Additional history from the patient and outside sources regarding previous level of functioning, other medications, prodromal symptoms, and recent intercurrent illness may be necessary. Other pertinent history should include the type of lithium preparation that was ingested and any underlying illnesses that predispose to toxicity. The diagnosis can be further complicated by the fact that many patients with toxicity on presentation may not have taken an intentional overdose of lithium, but rather may be suffering from chronic toxicity.

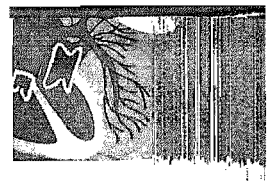
Physical Examination

Particular attention should be paid to the vital signs, degree of neurologic involvement, and cardiovascular status. Documentation of a thorough initial neurologic

TABLE 30-3 Serum Lithium and Toxic Manifestations[†]

SEVERITY OF SYMPTOMS	APPROXIMATE SERUM LITHIUM CONCENTRATION (mEq/L)	SYMPTOMS
No toxicity (therapeutic)	0.4–1.3	Usually none
Mild toxicity	1.5–2.5	Nausea, vomiting, lethargy, tremor CNS depression, fatigue, diarrhea
Moderate toxicity	2.5–3.5	Confusion, agitation, delirium, tachycardia, hypertonia
Severe toxicity	>3.5	Coma, seizures, hyperthermia, hypotension

*Lithium toxicity may be manifested even at therapeutic levels, especially in the elderly, when the therapeutic level may be 0.2 mEq/L.
[†]Classification of Hansen and Amdisen.[4] (Stages I and II: apathy, tremor, weakness, ataxia, motor agitation, rigidity, fascicular twitching, nausea, vomiting and diarrhea. Stage III: Latent convulsive movements, stupor, and coma.)



examination may be helpful in patients who may endure a prolonged hospital course.

Laboratory and Imaging Studies

Initial studies should include cardiac monitoring, electrocardiogram (ECG), assessment of oxygenation and monitoring of urine output, serum electrolytes, calcium, renal function, glucose, serum lithium level, and thyroid-stimulating hormone (TSH). Leukocytosis can be seen with therapeutic lithium use as well as intoxication. A low anion gap can also be present after acute ingestion of lithium carbonate[8] possibly owing to the presence of and interference by the carbonate anion in the calculation of anion gap. In addition, in chronic poisoning, patients are likely to demonstrate evidence of renal insufficiency with elevated blood urea nitrogen and creatinine. In some cases in which the diagnosis is initially unclear, imaging of the brain may be necessary. Although some formulations of lithium may be radiopaque, radiography is not reliable for excluding ingestion.[39]

Many hospitals have readily available serum testing for lithium levels (normal range, ~0.6 to 1.2 mEq/L). Serum levels should ideally be drawn at least 6 to 12 hours after the last therapeutic dose to avoid misinterpretation of predistributional levels. However, these levels can still be misleading because lithium has a low therapeutic index and levels frequently do not correlate with level of toxicity. Levels as high as 10.6 mEq/L (10.6 mmol/L) have been reported without evidence of neurologic toxicity after an acute overdose[40] because of the multicompartment kinetics of the drug. Furthermore, a normal level does not exclude toxicity, because serum levels do not accurately reflect the intracellular concentration or toxicity of the drug.

It is important to note that some specimen tubes contain lithium heparin as an anticoagulant and can falsely elevate serum lithium results. This phenomenon has been demonstrated to factitiously elevate serum lithium levels by as much as 2.0 mEq/L in healthy volunteers.[41] Others have reported these tubes producing falsely elevated levels by as much as 6 to 8 mEq/L.[42]

There is relatively poor correlation between serum levels and systemic toxicity, particularly after an *acute* or *acute-on-chronic* overdose. Hansen and Amdisen described 23 patients with lithium intoxication and concluded that there is *no clear-cut relationship between serum lithium levels and severity of symptoms*. However, 21 of their patients were suffering from chronic lithium intoxication. They suggested that levels of 1.5 to 2.5 mEq/L are associated with mild symptoms of toxicity, 2.5 to 3.5 mEq/L are considered serious, and greater than 3.5 mEq/L are considered life threatening (see Table 30-3). These levels, which were all drawn at approximately 12 hours after the last dose of lithium,[43] hold relevance only for patients with chronic lithium exposure.

Bailey and McGuigan prospectively studied all cases of lithium exposure brought to the attention of a poison control center over a 1-year period, and their study group included patients with acute, acute-on-chronic, and chronic exposures plus one patient with *severe* lithium intoxication after a chronic exposure and a peak serum level of 1.5 mEq/L.[44] They noted that toxicity occurred at lower levels in patients with chronic exposures compared with those with acute-on-chronic exposures. They concluded that the Hansen and Amdisen classification is not a useful tool for predicting morbidity or mortality and does not correlate well with lithium level.

Oakley and colleagues conducted a retrospective analysis of 97 cases of lithium exposure at a regional center over a 13-year period. They concluded that peak serum levels are significantly higher in patients with severe intoxication and that chronic exposure carries a substantially higher risk of severe neurotoxicity than acute exposure. Furthermore, they identified risk factors contributing independently to the development of chronic intoxication: NDI, age over 50 years, thyroid dysfunction, and baseline endogenous creatinine clearance below normal.[45]

Currently, most authors agree that clinical symptoms are more reliable than serum lithium levels. Additionally, management should be based on these clinical parameters rather than on drug levels.[46] Clinicians are cautioned about reliance on an isolated serum lithium level.

It has been suggested that erythrocyte, urine, or cerebrospinal fluid (CSF) levels of lithium might be useful in the assessment of lithium toxicity. The erythrocyte concentration does not fluctuate as much as plasma lithium levels, perhaps reflecting an intracellular lithium concentration. However, this value has not been shown to have clinical significance. CSF levels are about 40% to 50% of plasma lithium levels, but in animal studies they have demonstrated no advantage over plasma lithium levels in assessing toxicity.[47] In addition to being more invasive, CSF levels do not reflect intracellular levels of lithium. Urine levels do not correlate with clinical toxicity but can be useful in the calculation of renal lithium clearance.

Differential Diagnosis

Differential diagnosis of lithium toxicity includes psychosis, hypoglycemia, meningitis, encephalitis, gastroenteritis, food poisoning, drug withdrawal, intracranial bleeding, trauma, thyrotoxicosis, Parkinson's disease, and neuroleptic malignant syndrome. Intoxication by other psychotropic drugs that may be available to the patient should be considered, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), valproic acid, and antipsychotic drugs.

MANAGEMENT

Supportive Measures

Initial treatment of lithium toxicity includes appropriate airway management, assessment of vital signs, and continuous cardiac monitoring. Peripheral IV lines should be inserted for the administration of fluids as well

as other general emergency treatment measures including dextrose and naloxone if needed. Hyperthermia or hypothermia should be treated appropriately. If seizures develop, they should be treated with standard measures including benzodiazepines and barbiturates (see Chapter 2A). Electrocardiographic findings such as flattened or inverse T waves and mild QT prolongation do not usually require treatment; however, severe arrhythmias should be treated with usual measures, including magnesium for marked QT prolongation or torsades de pointes.

The goal of fluid therapy is to maintain GFR and urine output in order to reduce the continued reabsorption of lithium. Fluid replacement should begin with isotonic saline. A few reports have suggested marked improvement with forced diuresis using very large volumes of normal saline along with diuretics,[48] achieving lithium clearance values of 39 mL/min (in patients with normal renal function).[49] However, other studies have suggested less than favorable outcomes with forced diuresis, including a reduction in lithium clearance.[43] Because of inconsistent results and the risk of electrolyte imbalances, forced diuresis is not recommended. On the other hand, volume resuscitation to replace fluid losses and to maintain adequate urine output is crucial to the treatment of lithium intoxication.

Decontamination

There is no known antidote for lithium, so particular attention should be paid to gastric decontamination. Although it has been demonstrated in in vitro studies that lithium does not bind well to activated charcoal,[50] charcoal should be given if co-ingestants are suspected. In patients with early presentation, consideration should be given to gastric lavage, especially for regular-release preparations. After ingestion of sustained-release preparations (e.g., Litho-Bid), whole bowel irrigation may be preferable. In a crossover study of healthy volunteers who were given GoLYTELY at 2 L/hr for 5 hours after lithium ingestion, there was a significant reduction in peak lithium concentrations by more than 50% and reduction in lithium absorption by 67%.[51] Whole-bowel irrigation should also be considered after massive ingestion of regular-release products.

Limited evidence supports the use of sodium polystyrene sulfonate (SPS; Kayexalate) to bind lithium in the gut and to enhance elimination. Animal studies have demonstrated that the SPS resin effectively binds lithium and can reduce serum lithium concentrations even after IV lithium dosing.[7] Studies in healthy human volunteers have shown small but statistically significant reductions in lithium absorption after treatment with SPS, without significant changes in serum sodium or potassium levels.[52,53] However, the reductions were not large enough to likely affect the clinical course of an acute overdose.[52] Furthermore, there is no consensus regarding optimal dosing or whether electrolyte alterations in a sick patient population could be more pronounced. At this time, SPS is not recommended for acute lithium ingestion.

Elimination

Besides hemodialysis, a variety of methods have been suggested or reported to enhance the elimination of lithium, including alkaline diuresis, IV theophylline, and dopamine. However, in addition to posing potential adverse effects, these alternative methods are not supported by clinical studies.

Lithium renal clearance can be estimated using the serum and urine lithium levels. Renal lithium clearance = urine flow rate (mL/min) × urine lithium (mEq/L)/serum lithium (mEq/L). The normal renal lithium clearance is estimated to be between 10 and 40 mL/min. Hansen and Amdisen, however, reported in their study of chronic lithium intoxicated patients that the lithium clearance of this group ranged from 0.9 to 18.4 mL/min.[43] Similar variable clearances for patients on chronic lithium therapy have been found in other studies.[54]

Peritoneal dialysis has been shown to achieve lithium clearance rates of between 9 and 15 mL/min.[23,49] This modality might be considered in patients who have poor renal function if hemodialysis facilities are unavailable (e.g., in remote areas). Otherwise, it should not be substituted for hemodialysis.

Because lithium has a small volume of distribution and minimal protein binding, hemodialysis is an appropriate method for lithium removal. Lithium clearances of 70 to 170 mL/min have been reported with hemodialysis. However, there is controversy about indications for hemodialysis. Removal of lithium from the plasma and extracellular fluid may have little effect on intracellular lithium concentrations, and toxic effects may persist even after serum levels fall. This is consistent with the clinical observation that serum lithium levels correlate poorly with signs and symptoms of toxicity. It could be argued that dialysis is most likely to be effective soon after an acute ingestion while the serum lithium level is markedly elevated and prior to intracellular redistribution. However, these patients generally experience less severe toxic effects,[45] and patients with levels as high as 10.6 or higher[40] may remain asymptomatic and recover with supportive measures alone.

Amdisen recommended that patients with impaired renal function or those who have taken an overdose and have persistent levels greater than 1.4 mEq/L should undergo hemodialysis.[6] Jaeger and coworkers studied the kinetics of lithium in intoxicated patients and concluded that no rigid indication for hemodialysis can be set. They further stated that hemodialysis is not an emergency therapy but one that should be initiated only after observation of the patient as an inpatient and based on a combination of clinical and kinetic criteria.[54] Other authors have suggested that the rapid correction of lithium by hemodialysis might contribute to persistent neurologic toxicity similarly to rapid correction of hyponatremia.[28]

Bailey and McGuigan in a prospective study recommended hemodialysis for patients with any of the following criteria: (1) severe toxicity, (2) alteration in level of consciousness, (3) cardiac toxicity, (4) creatinine greater than 2.3 mg/dL associated with an acute lithium level greater than 2.0 mEq/L or chronic level greater

than 1.5, or (5) creatinine greater than 1.7 mg/dL associated with a chronic level of 2.5 mEq/L or acute level of 4.0 mEq/L. Serum creatinine levels were obtained after several hours of hydration. The authors compared the outcomes for patients in whom dialysis was recommended but not performed to those of patients who actually received hemodialysis. Although fewer patients received dialysis than was recommended, there was no outcome difference between the two groups. They concluded that indications for hemodialysis should be based on clinical symptoms and reserved for the more severe cases.[55]

Clearly, there is no consensus on precisely when to dialyze. Most agree that patients exhibiting signs and symptoms of severe lithium poisoning (seizures, coma, cardiac arrhythmias) or who have renal failure should undergo hemodialysis. In addition, dialysis should be considered in acute overdose patients with clinical deterioration and patients with chronic lithium toxicity whose serum levels are greater than 3.5 mEq/L. Patients with acute or acute-on-chronic overdose with elevated levels but who are asymptomatic or minimally symptomatic and have normal renal function should be treated with IV fluids and monitored closely for deterioration. There may be rebound (Fig. 30-2) in serum levels after dialysis, and the procedure should be repeated until the serum level 6 to 8 hours after dialysis is less than 1 mEq/L.

Several case reports have demonstrated success in adults and children[56] for treating lithium intoxication with the use of continuous renal replacement therapy (CRRT). This includes methods such as continuous venovenous hemodialysis (CVVHD), continuous arteriovenous hemodialysis (CAVHD), continuous venovenous hemodiafiltration (CVVHDF), and continuous arteriovenous hemodiafiltration (CAVHDF). The reported lithium clearance rates for CVVHD, CVVHDF, CAVHD, and CAVHDF are given in Table 30-4.[56-60] While these clearances are less than for hemodialysis, the procedures require less specialized staff and facilities and can be done continuously for several hours or days, compared with typical dialysis runs of 2 to 3 hours at a time. In addition, CVVHD is pump-driven and therefore does not rely on the patient's arterial pressure to provide a pressure gradient. One particular case study documented success with CVVHD in a hemodynamically unstable lithium-intoxicated patient in whom hemodialysis had to be discontinued.[58]

CRRT has the added advantage of ease of implementation and avoidance of rebound lithium levels (see Fig. 30-2). One author suggests that the combination of hemodialysis and CVVHD may have the potential to decrease length of hospital stay and health care costs.[56] CRRT procedures have been used for periods of 14 to 72 hours, with an average duration of 34.7 hours in one study.[60] It is not yet clear, however, whether CRRT will shorten the length of hospital stay or change outcome when compared with intermittent hemodialysis. There are no controlled studies to date comparing safety and efficacy of CRRT over other methods of therapy for routine treatment of lithium toxicity. Continuous renal replacement therapy may be considered in treating patients in facilities in which dialysis is not readily available or who are considered too unstable for immediate hemodialysis.

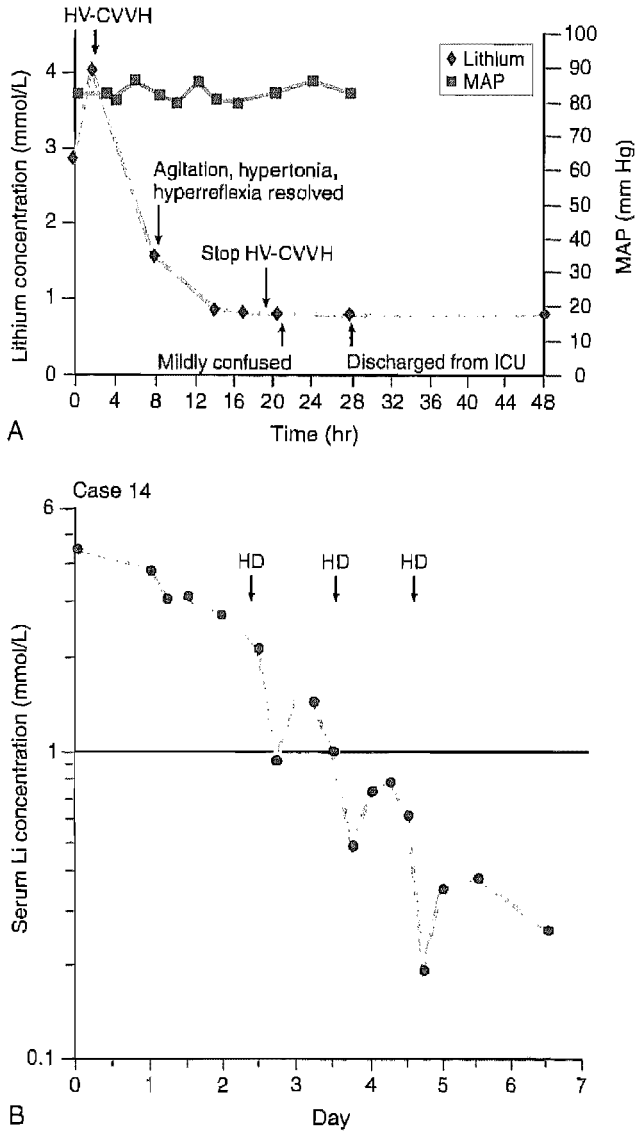


FIGURE 30-2 Serum lithium concentration after (A) high-volume continuous venovenous hemofiltration (HV-CVVH) vs. (B) intermittent hemodialysis (HD). Note the steady decline in lithium concentration during HV-CVVH in A in contrast with the rebound in lithium concentration after each run of hemodialysis in B. Although hemodialysis remains the gold standard for lithium elimination, other modes of continuous renal replacement therapy demonstrate promise. (Reproduced from Jaeger A, Sauder P, Kopferschmidt J, et al: When should dialysis be performed in lithium poisoning? A kinetic study in 14 cases of lithium poisoning. J Toxicol Clin Toxicol 1993;31:429–447, and van Bommel EF, Kalmeijer MD, Donssen H: Treatment of life-threatening lithium toxicity with high-volume continuous venovenous hemofiltration. Am J Nephrol 2000;20:408–411.)

Disposition

All patients with symptoms of lithium intoxication should be admitted to the hospital for observation in a

TABLE 30-4 Approximate Clearance of Lithium Based on Different Methods*

METHOD OF LITHIUM CLEARANCE	APPROXIMATE CLEARANCE (mL/min)
Normal renal clearance in healthy patient	10–40 mL/min
Renal clearance of patients taking lithium chronically	0.9–18.4 mL/min
Peritoneal dialysis	9–15 mL/min
Hemodialysis	70–170 mL/min
CVVHD	23–54 mL/min
CVVHDF	28–62 mL/min
CAVHD	20.5 mL/min
CAVHDF	27–55 mL/min

*Approximate clearances are based on data from references 56 to 60. CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; CAVHD, continuous arteriovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltraton.

monitored setting, even in the presence of normal serum lithium levels. Patients with moderate or severe symptoms should be admitted to an intensive care unit. For patients who are asymptomatic after an acute ingestion, serial levels should be obtained at 6-hour intervals until a downward trend has been established. Patients should not be discharged until they are asymptomatic and have a serum lithium level less than 1.5 mEq/L.

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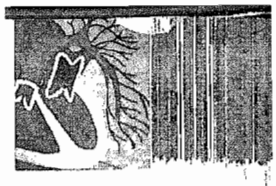

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