CHAPTER 160

LITHIUM

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PERSPECTIVE

Lithium has been used as a medicinal agent since the mid-1800s, when lithium salts were popularized as a treatment of gout (lithium carbonate and lithium citrate), a sedative for manic patients (lithium bromide), and a treatment of epilepsy (lithium bromide). In 1929, the soft drink 7UP, whose original name was Bib-Label Lithiated Lemon-Lime Soda, included lithium citrate (an ingredient until 1950) and was marketed as a patent medicine to cure hangovers. In the late 1940s, lithium chloride was used as a salt substitute for patients requiring low-salt diets. However, in 1949, the Food and Drug Administration (FDA) banned the use of lithium because of several patient deaths attributed to lithium toxicity. Ironically, in the same year, the Australian psychiatrist John Cade convincingly demonstrated the efficacy of lithium for the treatment of bipolar disorder. Use of lithium was prohibited in the United States until 1970, when the FDA reversed the ban on lithium and approved its use for the treatment of bipolar disorder. Despite the introduction of newer and safer medications, lithium remains the most effective long-term treatment to prevent recurrences of mania and bipolar disorder.[1] Lithium treatment also appears to substantially decrease the risk of suicide and suicide attempts.[1] According to U.S. Poison Control Centers data, in 2009, there were 6396 reported lithium exposures with 134 major outcomes (life-threatening or significant residual disability) and 3 deaths.[2] A very low mortality was also described in a retrospective study from 2003 to 2007 of lithium exposure cases reported to the California Poison Control System. The study identified 629 toxic exposures: 44 acute exposures, 124 acute-on-chronic overdoses, and 282 chronic overdoses. Of these patients, 69 patients required hemodialysis, and 4 died.[3]

PRINCIPLES OF DISEASE

The precise mechanism of action of lithium as a mood-stabilizing agent is still not fully understood. Lithium increases serotonin release and serotonin receptor sensitivity and also inhibits norepinephrine and dopamine release from nerve terminals. Postulated mechanisms have begun to focus on cellular pathways, including intracellular signaling, neuronal plasticity and neurogenesis, and gene expression. These mechanisms include the inositol depletion hypothesis, glycogen synthase kinase 3 inhibition, and the arachidonic acid cascade hypothesis. In the inositol depletion hypothesis, lithium inhibits inositol monophosphatase, which depletes brain cell myoinositol and dampens phosphoinositide signaling.[4-6] Lithium's neuroprotective properties are attributed to its ability to inhibit glycogen synthase kinase 3. Finally, in the arachidonic cascade hypothesis, lithium reduces the amount of arachidonic acid recycled in brain cells. Bipolar disorder is thought to result from a hyperactive arachidonic acid cellular signaling cascade.

Immediate-release lithium is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations occur 0.5 to 3 hours after a single oral dose, with complete absorption within 8 hours. Sustained-release lithium preparations exhibit variable absorption, with a delayed peak of 6 to 12 hours. Ingestion of a single 300-mg lithium carbonate tablet increases the serum lithium level by approximately 0.1 mmol/L. After absorption, lithium distribution follows an open two-compartment model. Lithium is initially distributed in the extracellular fluid and then gradually is redistributed in various tissue compartments (preferentially the brain, kidney, thyroid, and bone). Brain lithium distribution may take up to 24 hours after absorption. Approximately 95% of a single dose of lithium is excreted by the kidney. Lithium is freely filtered by the glomerulus, with 80% of filtered lithium reabsorbed by the proximal renal tubule. Lithium renal elimination is increased by factors that decrease glomerular filtration rate (e.g., dehydration) or sodium concentration (e.g., hyponatremia). Medications such as nonsteroidal anti-inflammatory drugs, diuretics, and angiotensin-converting enzyme inhibitors may increase lithium levels by interfering with renal lithium elimination.

Chronic lithium therapy is also associated with the development of nephrogenic diabetes insipidus, resulting in hyponatremia and dehydration and increased lithium levels. Fluid resuscitation and lithium cessation are usually sufficient to reverse the effects of diabetes insipidus permanently. Lithium also inhibits the synthesis and release of thyroid hormone, but hypothyroidism is a rare complication (5% of all patients) of chronic lithium therapy. Finally, lithium causes a temporary leukocytosis and was once investigated as a potential treatment of chemotherapy-induced neutropenia.

CLINICAL FEATURES

Clinical manifestations of lithium poisoning can be classified on the basis of whether the poisoning is due to acute toxicity, chronic toxicity, or acute-on-chronic toxicity.

Acute toxicity represents an overdose of lithium in a patient without any lithium body stores. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are the earliest and most common presentation of toxicity. Lithium also causes electrocardiographic effects, including bradycardia, T wave flattening or inversion, and QT prolongation. Several case reports have also reported lithium-induced Brugada-type electrocardiographic changes. Fortunately, significant cardiac dysrhythmias after lithium poisoning are rare. Neurotoxicity is delayed because of the time required for lithium to be distributed to the brain.

In chronic toxicity, the patient, who takes lithium regularly and has significant lithium body stores, develops toxicity because of increased absorption or, more commonly, decreased lithium renal elimination (e.g., dehydration, drug interactions, and renal insufficiency). Neurotoxicity is the predominant presentation. Mild toxicity may be manifested as a worsening tremor. Progressively more severe signs of neurotoxicity include drowsiness, hyperreflexia, confusion, clonus, coma, seizures, and extrapyramidal signs. The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is described as neurologic dysfunction attributed to lithium toxicity persisting for 2 months after lithium cessation.[7] Typical SILENT presentations include cerebellar dysfunction, persistent extrapyramidal syndromes, brainstem dysfunction, and dementia. The presence of fever is considered a poor prognostic sign and possible precipitant of SILENT.[7]

Finally, in acute-on-chronic toxicity, a patient who is already taking lithium ingests an additional quantity of lithium in excess of the prescribed dosage. The clinical presentation includes signs and symptoms of both acute and chronic toxicity, including gastrointestinal and neurologic symptoms.

Lithium use has also been implicated in the development of both neuroleptic malignant syndrome and serotonin syndrome. Serotonin syndrome usually results from the combination of serotonergic agents. Consequently, lithium should not be used in conjunction with serotonin agonists (e.g., monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, dextromethorphan, buspirone, and meperidine). Lithium use is also considered a risk factor for neuroleptic malignant syndrome. The signs and symptoms of neuroleptic malignant syndrome, serotonin syndrome, and lithium toxicity are similar, with considerable overlap of symptoms (fever and neurologic deterioration). Fortunately, the initial treatment of lithium toxicity, serotonin syndrome, and neuroleptic malignant syndrome is the same and includes supportive care and discontinuation of the involved medication.

DIAGNOSTIC STRATEGIES

Because the signs and symptoms of lithium toxicity are nonspecific and are often delayed after acute overdose, a serum lithium level should be obtained in any patient thought to have acute or chronic lithium poisoning. It may be helpful in patient management to obtain serum electrolyte values. Increased serum sodium concentration may indicate lithium-induced nephrogenic diabetes insipidus, whereas the serum creatinine level may help determine whether dialysis is required. Thyroid function studies should also be obtained if clinical thyroid disease is suspected. Finally, for acute, intentional ingestions, electrocardiography and determination of a serum acetaminophen level should be considered to evaluate for the presence of coingestants.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for lithium poisoning is extremely broad because of its nonspecific signs and symptoms. Consideration of an alternative diagnosis can be based on whether the clinical presentation represents acute versus chronic lithium poisoning. Acute lithium poisoning typically is manifested with initial, prominent gastrointestinal symptoms similar to those of other drug overdoses. These include other metal salts (e.g., iron, arsenic, or mercury), salicylates, cardioactive steroids (e.g., digoxin), and, rarely, theophylline. Other illnesses causing nausea and vomiting include gastroenteritis and other abdominal maladies. Chronic lithium poisoning, with its predominant neurologic symptoms, should raise concern for other neurologic conditions causing tremor or confusion and for central nervous system toxins, including central nervous system depressants, drugs that cause seizures, hypoglycemic agents, carbon monoxide, neuroleptic malignant syndrome, and serotonin syndrome.

MANAGEMENT

There is no antidote for lithium poisoning; consequently, the management of lithium toxicity includes selected gastrointestinal decontamination (for acute overdose only), techniques to increase the elimination of lithium (renal and extracorporeal) from the body, and supportive care.

Gastrointestinal Decontamination

Both oral activated charcoal and gastric lavage are ineffective in the management of lithium poisoning. Lithium is poorly adsorbed by activated charcoal.[8] Gastric lavage is ineffective for several reasons. The immediate-release lithium preparations are usually absorbed from the gastrointestinal tract too quickly for lavage or whole-bowel irrigation to be effective. Lithium-induced emesis typically occurs soon after an ingestion of immediate-release lithium, thereby limiting its own gastrointestinal absorption and making any attempt at gastric lavage potentially hazardous. Finally, sustained-release lithium tablets are too large to fit through an orogastric tube.

Whole-bowel irrigation with polyethylene glycol is the recommended gastrointestinal decontamination treatment for any overdose of sustained-release lithium preparation. It has not been studied in overdose but has been demonstrated to safely eliminate lithium in humans.[9] The recommended initial rate of administration is 2 L/hr in adults and 500 mL/hr in children through a gastric tube until the rectal effluent is clear (4-6 hours), but the rate may be decreased for vomiting.

Sodium polystyrene sulfonate (Kayexalate), a cationic exchange resin used to treat hyperkalemia, has been investigated as a gastrointestinal decontamination method for lithium poisoning. In animal models and in two human case reports (one volunteer and one overdose patient), administration of oral sodium polystyrene sulfonate (30 g every 6 hours for five doses) is effective in decreasing serum lithium levels.[8,10] However, it also significantly lowers serum potassium concentrations.[11,12] Because of limited patient experience and concerns about life-threatening hypokalemia, sodium polystyrene sulfonate is not recommended.

Techniques to Increase Elimination

Lithium can be removed by increasing renal elimination as well as by extracorporeal methods.

Fluid resuscitation with sodium chloride (normal saline) to correct hyponatremia and dehydration is the recommended method to maximize renal lithium elimination. Unless there are contraindications to aggressive volume expansion (e.g., renal insufficiency, congestive heart failure), administration of intravenous normal saline at a twice maintenance rate is recommended. Overly aggressive hydration, known as forced diuresis, is not recommended because of the risk of causing hypernatremia and because of its unpredictability in increasing renal lithium elimination. Urinary alkalinization by intravenous sodium bicarbonate is also not recommended because it does not significantly increase renal lithium elimination more than volume expansion by sodium chloride (normal saline) and because of the additional risk of hypokalemia and alkalemia.

The most effective technique to eliminate lithium from the body is hemodialysis. Endogenous lithium renal clearance is approximately 15 to 20 mL/min, whereas hemodialysis lithium clearance is approximately 100 mL/min.[13] Although hemodialysis substantially increases lithium elimination, its effect to decrease mortality or to treat or to prevent SILENT has never been

demonstrated.[13-16] Consequently, there is no evidence-based consensus to define the indications for hemodialysis for lithium poisoning. Hemodialysis is primarily used for clinical deterioration (e.g., seizures and decreased level of consciousness), inadequate endogenous lithium clearance (e.g., renal insufficiency), or inability to enhance renal elimination through volume expansion (e.g., congestive heart failure, cirrhosis, pancreatitis, and sepsis). Although it may not correlate directly with toxicity, hemodialysis is often recommended for a serum lithium level above 4.0 mEq/L for acute toxicity and above 2.5 mEq/L for chronic toxicity, but dialysis is most efficient when the drug is still in the vascular space before distribution to tissues. Continuous renal replacement therapies (e.g., continuous venovenous hemodialysis) have also been successfully used to treat lithium-poisoned patients.[17] Although their clearance rates are inferior to hemodialysis, they can be used in place of hemodialysis in hemodynamically unstable patients as well as in conjunction with hemodialysis in stable patients.

Because of the two-compartment model of lithium distribution in the body, serial lithium levels need to be monitored repeatedly for increases after treatment because of redistribution from intracellular stores. In chronic lithium toxicity, rising lithium levels from the large tissue stores occur after hemodialysis, necessitating multiple hemodialysis treatments.

DISPOSITION

Hospital admission should be considered for any patient with suspected lithium poisoning with abnormal neurologic signs (e.g., increased tremor, hyper-reflexia, clonus, altered sensorium, or seizure) or for any asymptomatic patient after acute overdose with increasing lithium levels or decreasing renal function. In addition, hospitalization at a center with emergency dialysis capability is preferable.

KEY CONCEPTS

- Lithium toxicity can be acute, chronic, or acute-on-chronic and presents with nonspecific gastrointestinal and neurologic signs and symptoms.
- Consider lithium poisoning in any patient who is taking lithium and presents with an altered sensorium.
- Medications that impair renal function or environmental factors that lead to dehydration increase the risk of lithium toxicity.
- Consider hemodialysis in patients with worsening tremor, confusion, decreased consciousness, inadequate renal function or inability to tolerate volume expansion (e.g., renal insufficiency and congestive heart failure), or serum lithium level above 4.0 mEq/L in acute poisoning or above 2.5 mEq/L in chronic poisoning.
- Lithium has numerous drug interactions that may lead to adverse effects, including increased risk for lithium toxicity, increased lithium toxic effects, neuroleptic malignant syndrome, and serotonin syndrome.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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