Lithium is an alkali metal naturally found in minerals and seawater. Compounds of lithium salts, most commonly lithium carbonate, have been used for medicinal purposes since the 19th century. Historically, lithium has been used to treat a range of diseases, including gout and hypertension, but currently it is primarily used to treat bipolar disorder. In bipolar disorder, it is a common adjunct mood stabilizer for patients prone to manic episodes or suicide. With an estimated one to three percent of the world’s population suffering from bipolar disorder, lithium’s use is widespread.

Although widely used, lithium has a narrow therapeutic window and toxic levels can lead to a variety of systemic symptoms which confer significant morbidity. Ahead, we will review the pharmacology of lithium, outline its use in modern medicine, and discuss severe lithium neurotoxicity in order to highlight its presentation, diagnosis, and treatment.

MECHANISM OF ACTION

Most commonly used in the treatment of bipolar disorder, lithium may also be used in refractory depression and schizophrenia or as an adjunct mood stabilizer. A recent meta-analysis also showed that lithium might play an important role in reducing suicide in those with a mood disorder. Although Lithium’s specific mechanism of action as utilized to treat psychiatric disorders has not been entirely elucidated and remains partially unknown, several hypotheses exist. For example, some evidence points to lithium being synergistic with serotonin neurotransmission. One study showed that serotonin uptake and release by neurons in rat raphe nuclei were enhanced by greater than 20 percent with the addition of lithium when compared to controls. In addition to mediating neurotransmission and release, much of lithium’s therapeutic action may be related to a reduction in the oxidative stress associated with recurrent episodes of both mania and depression. Lithium has been shown to reduce both neuronal apoptosis and autophagy, while at the same time increasing neural protective proteins. Glutamate and dopamine neurotransmission is thought to be augmented by lithium, aiding in its effect on mood stabilization.

The main inhibitory neurotransmitter, GABA, plays an essential role in regulating both dopamine and glutamine. GABA levels are known to be decreased in those with bipolar disorder and low GABA levels lead to excitotoxicity, which is counteracted by lithium, contributing to its neuroprotective properties. Additionally, lithium also enhances the release of several neuroprotective proteins.

PATHOPHYSIOLOGY

As previously mentioned, lithium toxicity is not uncommon due to its narrow therapeutic index. Lithium toxicity presents with a variety of clinical manifestations including renal dysfunction, neurologic dysfunction, gastrointestinal symptoms, cardiac manifestations, and endocrine abnormalities. The mechanism for injury on each system is not completely known.

The most common complication of chronic lithium ingestion is nephrogenic diabetes insipidus (DI), which can be seen in as many as 20 percent of patients on lithium. Due to lithium’s renal excretion, any change in the glomerular filtration rate will affect serum lithium concentrations; for example, renal dysfunction, hyponatremia, NSAIDs, and diuretics can directly cause an increase in lithium levels. The half life of lithium is approximately 29 hours, but when the drug approaches toxic levels it can impair excretion by reducing the GFR by as much as 0-5mL/min within the first year alone. Lithium accumulates in the collecting tubules and interferes with the ability of ADH to increase water
permeability, leading to a drop in urinary concentrating ability by 15 percent over time. This is usually observed early on in the course of lithium ingestion and is reversible, but if lithium doses are not adjusted over time the damage can become irreversible. In addition, lithium competes with sodium and potassium channels interfering with ion transport in neurons, ultimately altering neurotransmitter activity. Serotonin and acetylcholine effects are increased, dopamine effects are diminished, and cyclic adenosine 5-monophosphate cannot accumulate. The changes of neurotransmitter activity are thought to cause the severe neurological sequelae of lithium toxicity. Neurotoxicity of lithium can persist despite falling serum levels of lithium. This is likely due to lithium’s ability to accumulate in the cerebral white matter.

Lithium toxicity can also develop because of drug interactions, such as atypical and typical antipsychotic. Occasionally, lithium toxicity can be mistaken for other syndromes associated with antipsychotic use. As stated previously, lithium increases serotonin metabolites in the CSF. Lithium toxicity in combination with SSRIs may lead to a serotonin-like syndrome. A similar mechanism is seen with neuroleptic malignant syndrome given the synergistic effects lithium has on neuroleptic drugs. In a meta analysis of lithium toxicity, one case presented with increased pulse rate, blood pressure, and temperature in a patient consuming a combination of lithium and a neuroleptic drug. It is important to consider polypharmacy as a contributor to the development of lithium toxicity.

PRESENTATION

The effects of lithium toxicity are diverse and varied: from a mild hand tremor to a comatose state, from nausea and vomiting to bradycardia and hypotension. While lithium toxicity can affect almost every system, the scope of this paper will focus mainly on the neurological side effects. There is no typical age or direct correlation with gender to indicate a predisposition for a patient to develop toxicity, though it has been seen in more females than males. While one would assume the higher dose of lithium would more commonly result in toxicity, most cases have been seen in patients on less than 2,000 mg/day and no study has been able to prove a direct correlation between serum lithium levels and the severity of neurotoxicity. It is thought that severe intoxication occurs with levels less than 3 mEq/L and greater 5 mEq/L can be fatal, but in one meta-analysis most cases of toxicity occurred with serum levels below 1.5 mEq/L.

Most patients with lithium toxicity only experience mild neurological side effects, such as a hand tremor. As toxicity becomes more severe, patients develop pyramidal, extrapyramidal, and cerebellar signs. Severe intoxication can lead to seizures, stupor, and coma with a 10 percent risk of permanent neurologic effects, especially cerebellar dysfunction. The more common cerebellar signs seen with lithium toxicity include ataxia and other gait abnormalities, myoclonus, hyperreflexia, and dysarthria. Disorientation, altered consciousness, and acute delirium is associated with acute lithium neurotoxicity. Some patients have presented with seizure-like activity and EEG changes do occur, mainly manifested as diffuse slowing. Patients with prior EEG abnormalities are thought to be at increased risk for neurotoxicity. Given the wide variety of clinical presentations, a grading system has been developed to determine the severity of lithium induced neurotoxicity (Table 1). There are three main types of lithium toxicity: acute, acute on chronic, and chronic. Acute is considered in any patient who is lithium naïve and consumes a large amount of lithium at once, acute on chronic is seen in patients who have been on chronic lithium and overdose, while chronic toxicity is a slow accumulation of lithium in patients who have a decreased ability to excrete the drug due to the its side effects. The severity of disease has been shown to have correlation with the type of lithium toxicity, with chronic toxicity resulting in the highest incidence of severe disease.

The longer symptoms persist, the greater concern for prognosis. If symptoms persist for more than two months after cessation of lithium, the patient is at an increased risk for developing permanent neurotoxicity. Irreversible neurotoxicity has the same clinical manifestations as reversible neurotoxicity, but results in demyelination of the cerebellum and loss of purkinje fibers. Some authors believe that patients with pre-existing brain pathology are at an increased risk for developing neurotoxicity, since the brain tissue has an increased affinity for lithium as well as a decreased ability to clear intracellular levels of lithium.

TREATMENT

The standard treatment strategy of lithium toxicity generally involves stabilization by primary survey, cessation of lithium administration or any medications that may reduce lithium elimination, hydration, gastrointestinal decontami-

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nation, and enhanced elimination via extracorporeal treatments of enteral treatments. However, due to the relatively long time course involved in lithium poisoning after presentation, it is not unreasonable in certain non-life threatening cases to choose a conservative course of action, while monitoring serum lithium levels and renal function, so that treatment can be adjusted as necessary. Regardless of the level of toxicity, patients should be admitted for hospitalization; the level of acuity is dependent on the severity of the symptoms. In severe situations, for example when seizure or altered mental status is present, the patient should be admitted to an intensive care unit for further management.

Once lithium toxicity is suspected, a primary survey should be rapidly conducted to carefully assess the patient’s airway and breathing. After the patient’s airway and breathing are stabilized, the primary concern should be restoring volume by administering intravenous normal saline; a patient in a hypovolemic state seems to benefit the most from this, as many will experience a large decrease in total body fluid as a direct result of polyuria and concomitant central and nephrogenic diabetes insipidus secondary to lithium use. Hydration also promotes the renal excretion of lithium. Total volume resuscitation should be at least two to three liters, assuming normal cardiac function. Sodium levels should be monitored closely, as hypernatremia may occur when large amounts of normal saline are administered.

It is essential to discontinue any form of lithium therapy once a diagnosis of toxicity has been made. Additionally, certain medications are known to decrease the renal excretion of lithium; these drugs include thiazide diuretics, angiotensin converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs. Although diuretics may be the causative agent for lithium toxicity, the use of loop diuretics, such as furosemide or amiloride, may be beneficial. Loop diuretics have the benefit of augmenting the fractional lithium clearance, while decreasing the absorption of lithium in the proximal convoluted tubule. However, due to the side effect profile of these agents, including the risk of electrolyte disorders and dehydration, most researchers do not currently recommend this form of therapy.

The next step in treatment is decontamination. There are two forms of this therapy that have been investigated for use in lithium toxicity, one being activated charcoal and the second being whole bowel irrigation (WBI). Activated charcoal is administered via nasogastric tube and acts by restricting the absorption of most toxins; however this form of treatment does not bind lithium ions and has been found to have little effect on outcomes of lithium poisoning. WBI restricts lithium absorption, while decreasing the bioavailability of the toxin, and removing residual lithium from the gastrointestinal tract. These forms of treatment may be best suited for individuals in the early phase of acute poisoning, when lithium is still being absorbed, in comparison to chronic lithium toxicity, which is not nearly as dependent on acute levels of lithium found in the gut.

In more chronic lithium toxicity or in acute toxicity that does not respond to decontamination, the goal would be enhanced elimination. The purpose of this treatment modality is to augment lithium clearance, decrease the severity of the intoxication, and potentially prevent chronic sequelae from developing. The two main modalities that are available currently are extracorporeal treatments, normally utilizing hemodialysis (HD) or hemofiltration, and enteral treatments, using sodium polystyrene sulfate (SPS); extreme caution must be exercised when using SPS, as there is a high risk of hypokalemia with use. The decision to perform hemodialysis is often dependent on the serum lithium levels, as well as the patient’s clinical condition and renal function. Some researchers have suggested hemodialysis is appropriate in any patient with a lithium level greater than 6mEq/L; a chronic lithium user who has a lithium level greater than 4mEq/L; any patient with renal insufficiency, severe neurologic compromise, or hemodynamic instability with a lithium level greater than 2.5-4mEq/L; any patient with a lithium level less than 2.5mEq/L with concurrent ESRD or who fails to reach lithium level less than 1mEq/L after 30 hours. However, there is no universally accepted guideline for initiating hemodialysis, and it is often at the discretion of the nephrologist and/or intensivist. Also of note, HD works to clear serum (extracellular) lithium from the body, but has no role in clearing intracellular lithium stores; this is of particular importance when HD is discontinued, as serum lithium levels may eventually rebound to levels seen prior to the initiation of HD.

PROGNOSIS

The prognosis of patients with lithium intoxication varies, ranging from no residual sequel to long lasting neurologic deficits. The spectrum of prognosis does not seem dependent on the treatment modalities, as case reports suggest that neurologic deficits may be seen following the most aggressive forms of therapy, including hemodialysis. Most cases of intoxication will have total recovery of all neurologic function after resolution of the acute phase of toxicity; only a small percentage of individuals will go on to exhibit some form of neurologic deficit or dysfunction. The most concerning long-term deficit or dysfunction of lithium toxicity is the Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT), a constellation of neuropsychiatric symptoms that follows lithium toxicity and may remain long after serum lithium levels return to normal, with a minimum persistence of at least two months. Characterized by brainstem dysfunction, cerebellar dysfunction, extrapyramidal symptoms and cognitive impairment, the symptoms of SILENT are thought to represent attenuated versions of
more severe deficits present during the initial phases of toxicity. Additionally, researchers have suggested the possibility of visual and auditory perceptual disturbances, as well. Case reports suggest that severe cases of SILENT syndrome may persist for years, with cerebellar symptoms being the most frequently reported; these symptoms include truncal ataxia, gait ataxia, and clumsiness involving motor activity. Furthermore, case reports suggest that pyramidal signs have a greater chance of complete resolution in comparison to cerebellar signs, with ataxia persisting the longest. Risk factors for persistent neurologic dysfunction include presence of fever during intoxication; rapid correction of hyponatremia or lithium levels; high serum lithium levels on presentation; coexisting illnesses, such as epilepsy, acute gastroenteritis, or chronic kidney disease; and concomitant use of other drugs, such as antipsychotics or epileptic agents.

Of note, it is important to monitor thyroid function following lithium intoxication, as hypothyroidism is a common phenomenon that occurs concurrently with lithium use, affecting approximately 20 percent of lithium users, and may be exacerbated during times of intoxication. Lithium is concentrated in the thyroid gland three to four times more than in plasma. It inhibits release of preformed thyroid hormone by alteration in tubulin polymerization and also by inhibition of the stimulatory effect of TSH on the CAMP pathway. The incidence of goiter with lithium treatment is estimated to be 30 percent to 55 percent, while the prevalence of hypothyroidism with lithium treatment ranges between six percent and 52 percent. Lithium has been associated with rare case of hyperthyroidism as well. One report noted that 20 percent of Lithium-treated patients have antithyroid antibodies, compared with 7.5 percent without Lithium treatment. The same study observed increased B-cell activity and a decreased ratio of suppressor to cytotoxic T-cells, as well.

CONCLUSION
Despite the diverse presentation of lithium toxicity, it remains a common drug to treat a multitude of psychiatric disorders. Given its prevalence in the community, it is important to recognize the initial presentation of lithium toxicity as further progression can cause development of permanent neurologic disorders and severe renal dysfunction. Finally, always consider drug interactions, especially with other antipsychotic medications as well as nephrotoxic agents, particularly since the combination of these drugs with lithium increases the risk of toxicity.

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