CE 1.0 ANCC Contact Hour

Lithium-Induced Neurotoxicity: A Case Study

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ABSTRACT

BACKGROUND: In patients presenting with neurological deficits, identifying the cause can be challenging. **METHODS:** This case study discusses a condition that is not commonly seen. **DISCUSSION:** Although lithium toxicity syndrome is not as familiar as other causes of neurological issues, this should be considered for any patient who presents with unexplained neurological deficits and a history of taking this medication. **CONCLUSION:** If toxicity is not recognized early, the patient can be left with irreversible neurological symptoms, also known as syndrome of irreversible lithium-effectuated neurotoxicity, which impacts quality of life or can even cause death.

Keywords: lithium toxicity, neurotoxicity, SILENT

CASE STUDY

Mrs R, a 70-year-old white woman, is admitted from the emergency department to the neurological unit with a variety of concerning symptoms. She was found on the floor in her apartment by a neighbor. She exhibited acute mental status changes and was very lethargic. The neighbor was not sure how long she was "down." At the time of the admission assessment on the unit, Mrs R cannot follow simple commands, track the examiner, and is nonverbal. She also has a generalized tremor. A single dose of an antiepileptic drug had been given in the emergency department for concern of possible seizure activity. Her only significant medical history is osteoarthritis, slight obesity, and bipolar disorder for which she is prescribed lithium and has taken this for more than 15 years. Mrs R's current lithium level is elevated at 2.1 mEq/L, greater than the maximum therapeutic level of 1 to 1.5 mEq/L. After a negative head computed tomography and a thorough examination, the physician considers several possibilities. The top 2 differential diagnoses include seizure activity/postictal state and lithium toxicity syndrome.

Background

Lithium, a mood stabilizer, has been in use since the late 1800s.[1] Initially, this drug was used to treat gout and various psychiatric disorders and, later, as a maintenance drug for bipolar disorder. Unfortunately, because of the narrow therapeutic index, without regular monitoring, lithium use can result in toxicity even at doses that are appropriate.[2] Chronic toxicity can occur without any changes to the patient's usual dose. Foulser et al[3] describe a case of toxicity in a patient whose lithium levels were in normal range and who had been stable on lithium for more than 20 years. Because of undesirable adverse effects, the Food and Drug Administration banned lithium from the 1940s to 1970.[1] The clinical use of lithium was limited until there were more accessible means of monitoring.[4] Now that better monitoring methods are available, lithium is again Food and Drug Administration approved, and evidence demonstrates that it is very effective in treatment of acute manic episodes, suicide prevention, and preventative maintenance in patients with bipolar disorders.[5] Although the exact mechanism is not known, multiple studies have shown that the use of lithium lowered suicide risk in mood disorders better than placebos or other drugs.[6]

Current Use

The use of lithium, although declining, is still widespread because of approximately 1% to 3% of the world's population being diagnosed with bipolar disorder.[7] Although newer drugs are available, lithium is still considered by some as a "criterion standard" in the treatment of bipolar disorder.[8] It is also an inexpensive alternative to some of the newer drugs.[9]

As a mood stabilizer, lithium acts on the central nervous system (CNS), but the exact mechanism of action is not known.[1] Lithium dosing can be challenging as the optimal dosage varies for individual patients. The drug has a slow onset of action and can take several weeks to reach therapeutic effect. It is neither

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protein bound nor metabolized, and 95% is excreted by the kidneys.[10] The most common maintenance dose is 300 to 600 mg 2 to 3 times per day. For acute mania, up to 900 mg per dose may be given. If the creatinine clearance is less than 50 mL/min, lower dosages should be used.[1,11] Careful dosing is most important in the older adults and patients where decreased renal function and polypharmacy can increase the risk of toxicity.[3] Therefore, it may be best to target the low end of the range in those patients.[3]

Lithium has a very narrow therapeutic range of 1 to 1.5 mEq/L and a maintenance range of 0.6 to 1.0 mEq/L.[3,11] Toxicity usually happens at levels of 1.5 or higher; however, symptoms of toxicity can occur in some patients even when serum levels are normal. Levels greater than 5 mEq/L can be fatal.[12] Frequent monitoring through laboratory testing is recommended every 3 to 6 months, and the use of lithium is contraindicated if therapy cannot be closely monitored.[5,11]

Regular monitoring is also needed to assess for other possible issues. For example, chronic lithium therapy can cause T-wave flattening on electrocardiography, inhibition of the thyroid hormone that could lead to hypothyroidism, and nephrogenic diabetes insipidus.[10] Lithium can also increase creatinine, thyroid-stimulating hormone, neutrophil, and glucose levels.[11]

Effects of Toxicity

Lithium toxicity continues to be a concern. In the United States alone, there were almost 7000 cases of lithium poisoning reported to the American Association of Poison Control Centers in the year 2016.[4] These cases are especially common in persons living with mental illness or the older adults who are more vulnerable and susceptible to overdose.[1]

Lithium toxicity can be unpredictable. Blood levels are not necessarily reliable in predicting toxicity or its severity.[12] Although serum lithium levels show blood concentration, this does not always correlate with levels in other parts of the body.[3] Serum levels only reflect extracellular concentration, although intracellularly, the highest accumulation is in the brain and kidneys.[10] Depending on the timing of the last dose, levels can be normal in the serum yet elevated in the CNS.

Lithium toxicity can present with nonspecific symptoms such as nausea, vomiting, and diarrhea.[4] Early signs of toxicity may be missed and can be fatal.[10,12] Although this drug potentially affects the renal, endocrine, gastrointestinal, and cardiovascular systems, the CNS is impacted the most.[1,13] This is especially true in those patients who develop chronic lithium toxicity that develops gradually.[4] Neurological effects caused by lithium can range from a simple benign tremor to acute neurotoxicity, which can include ataxia, dysarthria, seizures, encephalopathy, and coma.[14] There are 3 categories used to describe lithium toxicity types: acute, chronic, and acute on chronic (Table 1). Of these, the acute on chronic is the most severe form with the greatest risk of irreversible long-term consequences.[10] There are also 3 levels of severity: mild, moderate, and severe (Table 2). Strategies that are used for other types of poisonings such as intravenous lipid administration or activated charcoal are not very effective for lithium overdose.[16] For treatment of severe toxicity, hemodialysis may be needed.[10]

The causes of toxicity are either due to an increased uptake or decreased excretion of the drug. For example, fluid or sodium loss can increase the concentration of lithium in the blood. Another example is elderly patients who are more vulnerable to toxicity, especially those with decreased kidney function.[4] Anything that causes excessive loss of fluid, such as fever, vomiting, or diarrhea, puts patients at a higher risk.[5] Interactions with other medications, especially those that increase lithium blood levels, can also increase risk. These include angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, calcium-channel blockers, and diuretics (especially thiazides).[5]

In a majority of cases, lithium toxicity is reversible, but persistent neurological symptoms may continue even after cessation of the drug.[9] If symptoms such as dementia, cerebellar impairment, and Parkinson-type syndromes persist 2 months or more after drug cessation, toxicity is labeled irreversible.[12] In rare cases, this causes permanent damage and is known as the syndrome of irreversible lithium-effectuated neurotoxicity

TABLE 1. Categories of Lithium Toxicity[1,10,15]

Category	Symptoms	History
Acute	Mainly gastrointestinal (GI) but can progress to neurological	Acute overdose, accidentally or on purpose Usually not on lithium therapy
Chronic	GI and neurological	On chronic therapy, taking too much over an extended period, but could develop because of volume depletion or renal impairment
Acute on chronic	Mainly neurological	On chronic therapy, but suddenly takes too much

TABLE 2. Grades of Lithium Toxicity Severity[10,15]

Grade	Symptoms	Serum Level
Mild	Nausea, vomiting, lethargy, fine tremor, fatigue	1.5–2.5 mEq/L
Moderate	Tachycardia, ataxia agitation, confusion, delirium, hypertonia	2.5–3.5 mEq/L
Severe	Hyperthermia, hypotension, seizures, renal failure, coma to death	>3.5 mEq/L

(SILENT).[14] Although the exact cause of SILENT is unknown, it is theorized that demyelination occurs at multiple CNS sites.[4] There are risk factors that may play a role in the development of SILENT.[14] These include alcohol use, infection/fever, hypertension, renal or heart failure, acute gastroenteritis, and epilepsy.

Implications for Practice

Early identification of lithium toxicity is imperative as many cases are preventable.[8] Nurses need to be aware of the signs and symptoms and watch for neurological changes. For patients who are prescribed lithium, education is essential. The education must include the importance of monitoring/blood work when on the drug, reporting any side effects or unusual symptoms to a healthcare provider right away, and recognizing risk factors. Patients should also notify their healthcare provider immediately if any of the following symptoms of possible toxicity occur: diarrhea, nausea/vomiting, drowsiness/altered mental status, blurred vision, slurred speech, ringing in the ears, muscle weakness/tremors, unsteadiness/coordination issues, or seizures. Patients need to know that toxicity could develop as a result of illness or heavy sweating. Patients should be cautious in hot weather, hot baths/saunas, or heavy exercising due to loss of fluid/sodium. Any patient with excess fluid loss is at risk for toxicity and should contact his or her healthcare provider so the dosage can be adjusted. An adequate fluid intake of 2500 to 3000 mL/d is recommended.[5] Sodium intake should be consistent because any changes in sodium intake may affect renal elimination of the drug.[11] Patients on lithium therapy should not be on low-sodium diets. They should also be careful with consumption of caffeine as this may decrease the lithium level and effects of the drug.[11]

As with any medication teaching, instruct patients to take the medication exactly as directed and in evenly spaced doses to keep blood levels constant. To decrease the possibility of gastrointestinal upset, lithium should be taken with or right after meals and with adequate amounts of water. Education should also be provided about drug interactions especially because some of these drugs that cause interactions (eg, nonsteroidal anti-inflammatory drugs) are available over the counter and commonly used.

Case Study Patient

Mrs R showed minimal improvement in the first 48 hours after her admittance to the neurological unit. Initially, the lithium dose was held. In addition to basic supportive nursing care, her neurological status was continuously monitored. The healthcare providers were worried that she may end up with residual neurological effects that could indicate the development of SILENT. In patients who receive previous lithium therapy, the risk for toxicity and prolonged neurological effects is higher.[16] Mrs R's generalized tremors continued, and an electroencephalogram (EEG) was ordered to rule out any seizure activity. The EEG revealed some slower brain activity. In some cases of lithium toxicity, the EEG can also show triphasic waves.[13]

After several days, Mrs R's lithium levels began to normalize and she started to verbalize, follow commands, and work with therapy. Luckily, she did not seem to have any irreversible neurological effects. After a 5-day hospitalization, she was discharged to a skilled nursing facility for further rehabilitation. An alternative to lithium may need to be considered for patients who live alone and have difficulties with management, but the long-term plan for Mrs R was for her to move in with her daughter. Both Mrs R and her daughter were provided with education about signs/symptoms of lithium toxicity and the importance of healthcare provider follow-up with routine blood work to monitor the levels.

Conclusion

Patients who present with neurological deficits can be difficult to manage, especially with the multitude of possible differential diagnoses. Some of these, such as lithium toxicity, are not common. However, it is extremely important for healthcare providers to recognize and treat lithium toxicity as soon as possible to prevent irreversible symptoms such as are seen with SILENT. Nurses play a key role in prevention and can make a difference through comprehensive neurological assessment, careful documentation of patient history, and continuing patient education.

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