Lithium and Antihypertensive Medication: A Potentially Dangerous Interaction

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A 62-year-old woman with hypertensive stage 3 chronic kidney disease and a long history of bipolar II disorder was hospitalized for progressive mental status change. A baseline serum creatinine was 1.3 mg/dL (normal, 0.8–1.2 mg/dL) and estimated glomerular filtration rate was 42 cc/min. Her hypertension had been well controlled while taking hydrochlorothiazide 25 mg daily for more than 5 years. Up until 5 years prior to admission the patient had multiple psychiatric hospitalizations, but since that time had achieved good stabilization on lithium carbonate 300 mg twice a day with a lithium level of 1.10 mEq/L (therapeutic, 0.3–1.3 mEq/L) 2 months prior to admission. There was no history of drug or alcohol abuse. She had a rash caused by carbamazepine and failed therapy with valproic acid and olanzapine.

Approximately 6 weeks prior to admission, with systolic blood pressures consistently 142 to 154 mm Hg, lisinopril 10 mg was added. A month later the patient's husband observed her to be weaker. It took longer for her to speak and she had more speech and movement hesitations. During the few days prior to admission, her voice appeared more strained and she seemed stiffer. Her thought process was noticeably slowed. Thinking that she was experiencing a bipolar exacerbation, her husband brought her to see her psychiatrist who referred the patient to the emergency department.

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On examination in the emergency department, her blood pressure was 126/62 mm Hg with a heart rate of 98 beats per minute and she was in no acute distress. She was able to follow some commands slowly and hesitatingly, but was also restless in bed and getting up on her hands and knees. Her eyes were frequently closed. The patient did not verbalize to the examiner but by report had a few normal sentences with a nurse. Another examiner noted her to be able to very slowly state her name and birth date. She was not fully cooperative, but was not stiff. Ataxia was noted, and moderate assistance for standing was required. Serum creatinine was 2.5 mg/dL and lithium level was 2.88 mEq/L.

Emergent hemodialysis with a bicarbonate bath was prescribed, and hydrochlorothiazide, lisinopril, and lithium were held. Shortly after hemodialysis her lithium level was 0.65 mEq/L, rising to 1.27 mEq/L 6 hours later, and a second hemodialysis was ordered. Eight hours following the second dialysis treatment, the patient's lithium level was 0.77 mEq/L. She was discharged on the fifth hospital day, back to baseline independent function, with a serum creatinine level of 1.6 mEq/L. Three months later the patient had a serum creatinine level of 1.2 mg/dL, a blood pressure of 132/78 mm Hg on amlodipine 5 mg daily, and a lithium level of 0.77 mEq/L on lithium carbonate 300 mg twice daily.

DISCUSSION

Scope of the Bipolar Disorders and Lithium Benefit

The spectrum of bipolar disorders has an estimated prevalence of 5%[1] and is frequently misdiagnosed as unipolar depression. A questionnaire survey of patients with diagnosed depression revealed a

mostly unsuspected bipolar diagnosis in 21.3%.[2] The diagnostic criteria for bipolar I include at least 1 manic episode with or without past major depressive episodes. Criteria for the more common bipolar II include at least 1 major depressive episode and at least 1 hypomanic episode, where hypomania is defined as an abnormal mood elevation lasting at least 4 days but not seriously impairing function.[3] In a careful prospective study of bipolar II, depressive symptoms dominated over hypomanic manifestations.[4]

Patients with bipolar disorder often have a shortened lifespan due to suicide mortality. Studies estimate that 25% of patients attempt suicide and that 11% eventually die of suicide.[5] Treatment is further complicated by a high rate of concomitant drug and alcohol abuse. Lithium treatment for bipolar disorders has commonly been used successfully since the US Food and Drug Administration's approval in 1970, with elucidation of a narrow therapeutic blood level range of 0.6 to 1.5 mmol/L following investigations begun by Schou and Baastrup in 1967.[6] Studies comparing lithium with newer agents such as carbamazepine, valproic acid, and antipsychotics demonstrate equivalent efficacy.[7,8] Lithium appears to have an additional advantage of decreasing suicide rates.[9] Therefore, there is a niche of patients with bipolar disease for whom chronic lithium treatment may be prolonging life, and for whom alternative therapy may not suffice.

Pharmacologic Features

The narrow therapeutic range of lithium and serious toxicity profile require knowledge of core pharmacologic concepts by primary care physicians as well as psychiatrists. Lithium is not bound to plasma proteins and distributes nearly evenly in the total body water space. The open 2-compartment intracellular/extracellular distribution model requires lithium level serum samples to be obtained at least 10 hours after an oral dose. Although peak lithium levels occur at 1 to 2 hours with twice-daily dosing and 4 to 5 hours following sustained-released once-daily dosing, samples assessing drug levels for both formulations should be obtained 10 to 12 hours postdosing.[10] Steady state levels are achieved 5 to 6 days following lithium initiation or a dose change, since the half-life under these conditions is about 20 to 24 hours.[11] Because lithium is not metabolized and is removed almost exclusively by renal mechanisms, blood concentrations are strongly affected by age, volume status, and underlying renal function. Conditions causing reduced plasma volume, such as gastrointestinal syndromes or hypotension, lead to increased proximal renal tubular reabsorption of lithium and potential toxicity. Factors leading to reduced renal function such as aging, heart failure, or chronic kidney disease also potentiate lithium toxicity.

Drug Interactions

Drug interactions, such as that which occurred in this patient, are the most important cause of serious lithium toxicity. Antihypertensive medications are commonly implicated. Thiazide diuretics have been shown to have the greatest propensity to induce this interaction because of their distal renal tubular site of action causing compensatory proximal tubular reabsorption of sodium and lithium. There have been many reports of lithium toxicity in patients coadministered thiazide diuretics, and studies looking at drug levels commonly report 20% to 40% increases in plasma lithium levels. Therefore, for a patient taking lithium started on a thiazide, a 40% decrease in lithium dose would be a safe approximation,[10] always checking a follow-up lithium level in 5 to 6 days. When considering a preemptory lithium dose adjustment, management of the underlying bipolar disorder should involve discussion with the prescribing psychiatrist. Gelenberg and colleagues[12] confirmed the observations of prior investigators, noting a 3-fold risk of relapse in patients with lithium concentrations of 0.4 to 0.6 mmol/L compared with patients with a range of 0.8 to 1.0 mmol/L.

In drug studies of healthy volunteers investigating pharmacologic effects, there are usually nonsignificant decreases in lithium levels when patients are coadministered furosemide and other loop diuretics, attributed to the distal renal tubular site of action of these agents that promote excretion of both sodium and lithium.[10] However, in a population-based nested case-control study involving patients 66 years and older, a dramatic increase in hospitalized cases of lithium toxicity was observed within a month of loop diuretic initiation (relative risk [RR], 5.5; 95% confidence interval [CI], 1.9–16.1) or an angiotensin-converting enzyme (ACE) inhibitor (RR, 7.6; CI, 2.6–22.0), but not with thiazide diuretics.[13] Thus, other previously noted patient factors such as volume status and renal function in sick elderly patients requiring loop diuretics are often more important than pharmacologic activity and predispose towards lithium accumulation.

The effect of angiotensin-converting enzyme (ACE) inhibitors on lithium excretion is variable

Table I. Medication Interactions on Lithium Levels Independent of Important Patient Factors Such As Volume Status and Chronic Kidney Disease
Increased lithium levels
Thiazides
Angiotensin-converting enzyme inhibitors
Nonsteroidal anti-inflammatory agents, except sulindac and aspirin
Spironolactone
Increased or decreased lithium levels
Loop diuretics
Calcium channel blockers
No demonstrated effect on lithium levels
Amiloride
Aspirin
Sulindac
Reduced lithium levels
Osmotic diuretics

Table II. Clinical Manifestations of Lithium Toxicity
Mild toxicity (serum lithium concentration= 1.5–2.0 mmol/L
Lethargy
Drowsiness
Coarse hand tremor
Muscular weakness
Nausea/vomiting
Diarrhea
Moderate toxicity (serum lithium concentration= 2.0–2.5 mmol/L)
Confusion
Dysarthria
Nystagmus
Ataxia
Myoclonic twitches
Electrocardiographic changes (flat or inverted T waves)
Severe toxicity (serum lithium concentration >2.5 mmol/L)
Grossly impaired consciousness
Increased deep tendon reflexes
Seizures
Syncope
Renal insufficiency
Coma
Death
Reprinted with permission from Finley et al. [10]

and reports of toxicity compared with thiazide diuretics are less common. Chronically or acutely ill patients with chronic kidney disease or who are volume depleted, and therefore more dependent on angiotensin II production for glomerular perfusion when prescribed ACE inhibitors, are probably more susceptible to lithium toxicity. In the current case discussion, this patient who had long-standing therapeutic lithium levels while taking hydrochlorothiazide and lithium developed toxicity about a month following initiation of lisinopril 10 mg. Underlying stage 3 hypertensive chronic kidney disease was probably a predisposing factor. Another contributing factor was the high therapeutic range drug level felt to be necessary to control this patient's bipolar disorder, which allowed little leeway. Acute renal insufficiency could have been caused by either the ACE inhibitor, lithium, or a combination of both.

Reports describing interactions with other antihypertensive agents are more limited and anecdotal. Calcium channel blockers may occasionally enhance lithium excretion,[10] and spironolactone slightly increases lithium levels due to a reduction in volume status.[10] Amiloride has been successfully used to treat lithium-related diabetes insipidus and, in those patients, lithium levels have remained stable.[10] β-blockers have been used to treat lithium-related tremor and lack a demonstrated effect on drug levels, but there is concern that in doing so, more serious lithium toxicity may be masked.[14] Nonsteroidal anti-inflammatory agents, with the exception of sulindac and aspirin, have been shown to increase lithium levels.[10,15] Table I summarizes the effects of antihypertensive agents on lithium levels, in the absence of patient-specific factors such as volume status, which may predominate with an acute illness.[15]

Spectrum of Lithium Toxicity

Patients with lithium toxicity present with neurologic, renal, gastrointestinal, and cardiac side effects, with neurologic effects predominating. As demonstrated by the current case discussion, the neurologic side effects may be confused with a breakthrough of the underlying psychotic disorder being treated. Our patient's husband brought her to the psychiatrist asking for more lithium. Manifestations of toxicity are also generally tiered according to drug level, as seen in Table II, but clinical symptoms are a better indication of toxicity than drug levels.[16] Early neurologic effects, characterized by lethargy, confusion, dysarthria, nystagmus, and ataxia are associated with moderate toxicity; reduced consciousness, seizures, and coma are at the severe end of the spectrum. In some cases, severe neurologic effects such as ataxia and dementia may be permanent despite decontamination.[17] Cardiac effects commonly include ST-T–wave changes and prolonged QT intervals. Rarely,

bradycardia, bundle branch block, ventricular tachycardia, ventricular fibrillation, and myocarditis occur.[16,18] Acute renal insufficiency may be seen with severe toxicity. Lithium-induced nephrogenic diabetes insipidus persists despite drug discontinuation, but is not an effect of toxic drug levels.

Treatment of Toxicity

Hemodialysis was necessary for the treatment of severe lithium toxicity in this patient, but hemodialysis is also indicated for lesser degrees of neurologic and renal dysfunction. Intravenous hydration with normal saline is indicated for volume depletion, but saline diuresis is not a recommended treatment for lithium toxicity. Mild neurologic effects can be reversed with discontinuation of lithium and interacting drugs. However, since 95% of lithium is renally excreted, moderate neurologic toxicity is a hemodialysis indication in the presence of renal insufficiency because the lithium will not be otherwise removed or degraded. Peritoneal dialysis is not recommended because it clears only 9 to 15 mL/min of lithium.[15] Dialysis is usually unnecessary with serum lithium levels <2.5 mEq/L, but postadmission levels may rise and need to be checked. The decision for dialysis should be made dependent on the patient's clinical status, renal function, and drug levels. Levels greater than 4 mEq/L usually require dialysis.[18] Lithium levels obtained 6 hours postdialysis may rebound because lithium in the intracellular space redistributes slowly into the plasma and long-acting time release preparations have prolonged gastrointestinal absorption.[15,18] Therefore, additional hemodialysis for lithium rebound may be necessary, as was the case with this patient. Indications for hemodialysis are: (1) lithium levels >4 mEq/L; (2) levels 2.5 to 4.0 mEq/L with severe symptoms, or with conditions such as chronic kidney disease, heart failure, or cirrhosis[15]; and (3) moderate clinical toxicity with significant renal impairment.[15,18] The goal is to achieve a lithium level 6 to 8 hours postdialysis <1.0 mEq/L to be reassured that rebounds will no longer occur and it is safe to discontinue dialysis.[16]

Summary

A patient with severe chronic lithium toxicity precipitated by the addition of lisinopril for the treatment of hypertension presented with severe neurologic symptoms and acute renal insufficiency requiring hospitalization for acute hemodialysis. The mean age of onset of bipolar I is 18 years and for bipolar II, 22 years.[19] A majority of patients with bipolar disorder have major symptoms before age 25, and onset is rare past age 60.[20] As these young patients with a controlled stable disorder become older, they are likely to develop hypertension and require therapy, which may cause a dangerous drug interaction. In the southern California Kaiser Permanente hypertension registry of 631,000 patients, 940 individuals (0.1%) also receive lithium. Even systematized reminders for these infrequent drug reactions require an awareness by primary care providers of the clinical patient factors that predispose to toxicity and the need to collaborate with the patient's psychiatrist. Diuretics and ACE inhibitors may be administered to patients taking lithium when 10- to 12-hour postdose levels are obtained 5 to 6 days following medication initiation or dosage change, with psychiatric follow-up.

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