Lithium-Induced Nephrogenic Diabetes Insipidus

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Background: **Lithium can cause nephrogenic diabetes insipidus in up to 20 to 40 percent of patients currently taking the medication, and a subset of these patients will have a persistent concentrating defect long after lithium is discontinued. They are at risk for serious hypernatremia when fluid intake is restricted for any reason.**

Methods: **MEDLINE as used to search the key words "nephrogenic diabetes insipidus" and "lithium" from 1990 to the present. A case report describes a patient who had been off lithium for 8 years and who developed hypernatremia after she was transferred to a new long-term facility and the staff attempted to control the patient's polydipsia. The diagnosis and treatment of nephrogenic diabetes insipidus are also discussed.**

Results: **This case of persistent nephrogenic diabetes insipidus 8 years after discontinuing lithium is the longest ever reported. Certainly, a number of patients have varying degrees of persistent lithium-related nephrogenic diabetes insipidus. Although pathologic changes are associated with persistent nephrogenic diabetes insipidus, the exact mechanism of the persistent defect is unknown. The mechanism of acute lithium-induced nephrogenic diabetes insipidus while the patient is on lithium is related to changes in intracellular cyclic adenosine monophosphate.**

Conclusions: **Patients currently taking lithium and patients with a remote history of lithium treatment need to be monitored for signs and symptoms of nephrogenic diabetes insipidus. Physicians need to be aware of the potential for nephrogenic diabetes insipidus in these patients and care for them appropriately.**
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Lithium has been shown to cause nephrogenic diabetes insipidus. As many as 20 to 40 percent of patients taking lithium have had symptoms related to a concentrating defect, and up to 12 percent have frank nephrogenic diabetes insipidus.[1] There also appears to be a sizable subset of patients with a persistent concentrating defect after lithium is discontinued.[2] These patients remain at risk for serious hypernatremia when their fluid intake is restricted, when they receive inadequate intravenous fluids perioperatively, or when they become acutely ill.[3] The risk to patients is easily missed or underestimated if the physician is unaware of current or past lithium use. In addition, effective treatment is available, which underscores the importance of recognizing which patients are at risk. This case report describes a patient who was admitted to the hospital for treatment of polyuria, polydipsia, and hypernatremia whose lithium therapy had been discontinued 8 years earlier.

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Methods

MEDLINE was searched from 1990 to the present using the key words "nephrogenic diabetes insipidus" and "lithium." A case report is presented of a patient who had stopped taking lithium for 8 years earlier and developed hypernatremia after transfer to a long-term facility, where the staff attempted to control the patient's polydipsia. Pathophysiology, diagnosis, and treatment of nephrogenic diabetes insipidus are then addressed.

Case Report

A 55-year-old woman who had a long history of bipolar illness and schizophrenia was admitted with a chief complaint of polydipsia and polyuria. Eight years before this admission she was evaluated for possible diabetes insipidus related to lithium treatment, at which time her lithium was discontinued and she improved. She was cared for intermittently since that time by various psychiatrists and generalists and had been well as long as she was allowed to drink as much as she wanted. The patient stated she drank approximately 20 to 40 glasses of water each day and voided "all day and all night long."

One month before her admission the patient moved into a supervised living home. Her case manager attempted to limit her fluid intake, which resulted in increased confusion and lethargy. She was seen in the emergency department and was found to have a sodium level of 156 mEq/L. She was treated with intravenous fluids for dehydration, her symptoms resolved, and she was released back to the supervised living home. Two weeks later her case manager referred her to the family practice residency for evaluation of persistent polydipsia and polyuria.

At the time of referral the patient was asymptomatic. Her medications included 2.5 mg of enalapril twice a day, three 250-mg doses of valproic acid at bedtime, 50 mg of trazodone at bedtime, 1.5 mg of risperidone twice a day, 5 mg of pilocarpine three times a day, an iron supplement twice a day, 500 mg of calcium twice a day, and 75 to 400 mg of phenylpropanolamine-guaifenesin twice a day as needed. Her medical history was notable for hypertension controlled with enalapril, asymptomatic multinodular goiter, and cholecystectomy in 1988.

When she was examined, her blood pressure was 116/76 mmHg and her weight was 50.5 kg. She was alert, oriented, and cooperative, and she did not appear to be confused. Findings during a head and neck examination were unremarkable, and her thyroid was nonpalpable. Her lungs were clear, her heart had a regular rate and rhythm, and there were no abdominal masses and no organomegaly. Results of a neurologic examination were normal except for a minimally wide-based unstable gate. Her pertinent fasting admission laboratory results were sodium 154 mEq/L, potassium 4.9 mEq/L, creatinine 1.8 mg/dL, calcium 9.8 mg/dL, prolactin 373 ng/mL, thyroid-stimulating hormone 1.11 μIU/mL, serum osmolality 297 mOsm/kg, and urine osmolality 141 mOsm/kg.

She was allowed to drink as desired during the day, and an 8-hour water restriction was started the first night of admission. Her initial 8-hour urine output, when fluids were not restricted, was 1.85 L and intake was 2.79 L. Her urine output during the 8-hour fluid restriction was 1.125 L. Her weight the morning after the 8-hour fluid restriction was 49.5 kg. The next morning laboratory test results were sodium 145 mEq/L, serum osmolality 305 mOsm/kg, and urine osmolality 124 mOsm/kg. She was subsequently given 20 units of vasopressin subcutaneously, and 2 hours later her serum osmolality was 304 mOsm/kg and her urine osmolality was 143 mOsm/kg (Table 1). These values were consistent with an unresponsive renal collecting system.

Table 1. Laboratory Results Before and After Fluid Restriction and After Vasopressin.

Component	Before Fluid Restriction	After Fluid Restriction	After Vasopressin
Weight, kg	50.5	49.5	n/a
8-h urine output, L	1.85	1.125	n/a
Serum osmolality, mOsm/kg	297	305	304
Urine osmolality, mOsm/kg	141	124	143

Because of the elevated prolactin levels, magnetic resonance imaging (MRI) of her head was ordered. It showed a normal sella but possible normal-pressure hydrocephalus. Subsequent cisternogram, neurologic evaluation, and neurosurgical evaluation determined the patient had cerebral atrophy, not normal-pressure hydrocephalus. The normal sella on MRI and the failure to respond to exogenous vasopressin ruled out central diabetes insipidus. Elevated prolactin levels have been reported in patients on risperidone (discussion with the Janssen Pharmaceutical representative, January 1997). Chlorthalidone was prescribed, 25 mg/d, and the patient was discharged. When she returned 1 month later to the outpatient clinic, her polydipsia had decreased, and she only rarely had nocturia. Her sensorium remained stable, and follow-up electrolyte measurements were within normal limits.

Discussion

This case report describes a patient with persistent nephrogenic diabetes insipidus related to lithium. Lithium, which has been and continues to be prescribed frequently, is used for treatment of psychiatric problems in up to 0.1 percent of the entire population.[1] If only a small percentage of these patients develop persistent nephrogenic diabetes insipidus, a great many patients would be at risk for related electrolyte disturbances.

In 1991 Boton et al[4] reported a lithium-induced inability to concentrate urine in 54 percent of patients on long-term lithium therapy. In other reports 20 to 40 percent of patients have had symp-

toms related to this concentrating defect, and 12 percent have had frank diabetes insipidus.[1] The frequent use of lithium and the incidence of the concentrating defect make lithium the most common cause of nephrogenic diabetes insipidus.[1] Even more important is the risk of persistent concentrating defects after lithium is stopped. Bucht and Wahlin[2] reported that 17 of 27 patients had persistent concentrating defects 1 year after stopping lithium. Patients currently taking lithium and patients who have stopped taking lithium could therefore be at risk for severe hypernatremia if they are given standard intravenous fluids perioperatively or for other unrelated medical problems.[3]

The effect of lithium on the kidney and its persistent effect after discontinuation have been debated in the medical literature. Although in the 1970s there was concern that lithium caused a permanent decrease in renal function and glomerular filtration rate, further studies failed to show a high incidence of chronic renal failure or decreased glomerular filtration rate.[5] Nevertheless, based on case reports and literature review, there does seem to be a subset of patients who during and after lithium therapy have persistent concentrating defects that might be associated with specific pathologic changes.[2,4,6-9]

Pathophysiology of Lithium-Induced Nephrogenic Diabetes Insipidus

When antidiuretic hormone (ADH) binds to its receptor on the basolateral membrane of the principal cell in the cortical and medullary collecting tubules, a guanyl-nucleotide regulatory protein (G protein) is activated. This action stimulates adenylate cyclase and increases intracellular cyclic adenosine monophosphate (cAMP). Water channels are then opened, and there is an increase in water permeability and absorption.[10,11] Lithium impairs the ADH-stimulatory effect on adenylate cyclase, resulting in less cAMP, which, in turn, decreases the diffusion of water through pores in the cell membrane of the collecting tubules. The final result is an inability to concentrate urine maximally.

The effect lithium has on cAMP can explain the acute effect of lithium on the renal tubules but cannot explain the persistent concentrating defect occasionally observed even after lithium is discontinued. Some authors suggest there might be a separate mechanism for the irreversible effect lithium has on concentrating ability after the drug is discontinued.[1,2,4]

The most recent literature review by Walker[8] summarizes the current view on the persistent irreversible concentrating defect caused by lithium. Patients taking lithium, especially those on long-term therapy, can develop an irreversible concentrating defect that can persist to varying degrees after lithium is discontinued. This defect is associated with a chronic tubulointerstitial pathologic change that can also be found in animal models with lithium. Some studies, however, have documented similar pathologic changes in psychiatric patients who had never taken lithium. Lithium and these pathologic changes are associated with persistent concentrating defects.[8] Patients with a glomerular filtration rate of less than 60 mL/min might be prone to the irreversible concentrating defect of lithium as reported by Neithercut et al.[7] Lithium, however, does not cause chronic renal failure or a decrease in the glomerular filtration rate.[8]

Diagnosis

Diabetes insipidus can be central or nephrogenic. Central diabetes insipidus is caused by a deficiency in vasopressin release from the posterior pituitary. The causes of central diabetes insipidus include a familial disorder; traumatic, postsurgical, or neoplastic disease; an ischemic or hypotensive episode; granulomatous disease; infections; autoimmune disorders; and idiopathic diabetes insipidus. Nephrogenic diabetes insipidus is caused by the inability of the kidneys to respond to vasopressin. Nephrogenic diabetes insipidus can be familial X-linked or caused by hypokalemia, hypercalcemia, obstructive uropathy, sickle cell trait or disease, amyloidosis, pregnancy, and drugs.[12]

There are three steps to diagnosing nephrogenic diabetes insipidus. First, the physician should take a careful medical history, perform a physical examination, and order screening laboratory studies, looking for the causes of diabetes insipidus listed above. The second step is water deprivation, which determines whether the patient has a concentrating defect. After baseline urine and serum osmolality and baseline electrolytes are measured, water is withheld for a 4 to 18 hours (usually 12 hours). Urinary output is monitored, and the patient is weighed before and after fluid deprivation. Serum and urine osmolality and elec-

trolytes are measured again after fluid deprivation. Normal patients have a two- to four-fold increase in urine osmolality.

The third step differentiates between central and nephrogenic diabetes insipidus. Five units of vasopressin are given subcutaneously after the water deprivation laboratory results are obtained. One to 2 hours later serum and urine osmolality is again measured. Patients with complete central diabetes insipidus fail to increase urine osmolality after deprivation and have a greater than 50 percent increase in urine osmolality after vasopressin administration. Patients with nephrogenic diabetes insipidus fail to increase their urine osmolality after deprivation and have a less than 10 percent increase in osmolality after vasopressin administration. Patients with a combined central and nephrogenic diabetes insipidus have a 10 percent or greater but less than a 50 percent increase in urine osmolality in response to vasopressin.[12]

The patient described in the case report had an erroneous partial response to vasopressin. Because her urine osmolality increased by 14 percent, we questioned whether she had a combined partial and central nephrogenic diabetes insipidus. A normal sella on MRI, however, is not consistent with a central component. In addition, the patient was inadvertently given 20 units of vasopressin, not the recommended 5 units, which probably explains the borderline increase in urine osmolality. An arginine vasopressin (AVP) radioimmunoassay is available at some reference laboratories and is useful for differentiating central from nephrogenic diabetes insipidus. An AVP assay might have been useful in the patient described. It was unfortunately not tested.

It is interesting to note that lithium has been reported to cause a combined central and nephrogenic diabetes insipidus. Posner and Mokrzycki[10] described a patient with combined central and nephrogenic diabetes insipidus while on lithium. They used AVP assays, as well as the other testing described above, to document the combined defect. The patient's central defect cleared, however, after stopping lithium, as shown by rising AVP levels. The nephrogenic concentrating defect persisted despite rising AVP levels. Because the patient described in the case report had not been taking lithium for 8 years, lithium was not considered to be a reason for the possible central defect.

Treatment

Treatment of lithium-induced nephrogenic diabetes insipidus in this article will focus primarily on long-term treatment for stable patients. Briefly, the treatment of acute hypernatremia in nephrogenic diabetes insipidus requires replacing the calculated total body water deficit with normal saline or hypotonic saline. Severely ill patients require normal saline to correct intravascular circulatory collapse and to prevent iatrogenic cerebral edema.[12]

Symptomatic, stable patients taking lithium who have nephrogenic diabetes insipidus can sometimes respond to a decrease in the dosage, or they improve after discontinuing lithium.[6] Not all patients continue to have concentrating difficulties after the medication is stopped. Some patients have a mild enough defect that it does not produce symptoms or require treatment. Persistent symptomatic polyuria and polydipsia, however, should be treated.

Diuretic and nonsteroidal anti-inflammatory medications have been used to treat lithium-induced nephrogenic diabetes insipidus. Diuretics decrease extracellular fluid and promote proximal tubular resorption, which is not dependent on ADH. The net result is less free water transmitted to the distal collecting tubules where the urine-concentrating defect is located and, therefore, less polyuria.[1,6] The two types of diuretics commonly used are amiloride and thiazides.

Amiloride has the advantage of being a potassium-sparing diuretic and does not require potassium supplementation. It also might prevent the uptake of lithium by the epithelial cells and theoretically prevent the inhibitory effect of lithium on ADH-mediated water transport.[4] Amiloride also has less potential than thiazides for lithium toxicity.[6] Amiloride, however, is less effective than thiazides because it induces less extracellular fluid contraction. Thiazide use can require potassium supplementation and is more often associated with lithium toxicity. Patients on lithium and diuretics need to have lithium levels monitored closely. Amiloride is usually started at 10 mg/d and can be increased to 20 mg/d.[1,6] Thiazides are prescribed in the same dose range used for treating hypertension. Patients who fail to respond to either diuretic can be given both amiloride and a thiazide, as they will sometimes have an additive effect.[6]

Diuretics have a gradual onset of action, which makes them less useful in an acute situation.[11] In-

domethacin has a rapid onset of action and can be appropriate for the initial therapy in the acutely ill patient. It is not, however, recommended for long-term use.[1,6] A dose of 50 mg three times daily is usually adequate. Two potential mechanisms explain the effect of indomethacin, and both are related to its antiprostaglandin effect. In rats prostaglandin inhibition increases cAMP in the collecting tubules, promoting water resorption.[11] Indomethacin also blocks the production of the prostaglandins that regulate glomerular blood flow and, therefore, decreases the glomerular filtration rate.[1] A decrease in the glomerular filtration rate results in less urine flowing to the distal tubule and less loss of free water. Indomethacin has been the primary nonsteroidal anti-inflammatory drug prescribed, but there is one case report of ketorolac being used intravenously in an acutely ill patient who failed to respond to indomethacin.[13]

Summary

Lithium is the most common cause of nephrogenic diabetes insipidus, and its effect is both reversible and irreversible. A concentrating defect can persist after lithium is stopped, in this case for at least 8 years. The irreversible effect might be associated with a specific pathologic lesion affecting concentrating ability, but the lesion does not cause a fall in the glomerular filtration rate. The long-term irreversible effect is important when treating patients who are hospitalized for surgery or medical problems. If they are not allowed to satisfy their thirst and are given standard intravenous fluid regimens, they can develop serious electrolyte problems.[3] The initial treatment is to adjust the lithium dosage or discontinue the medication regimen, assuming the psychiatrist is in agreement. Amiloride and thiazide diuretics, either alone or in combination, are the mainstay for long-term treatment. The acutely ill patient requires careful fluid management, and indomethacin is appropriate as well. Indomethacin, however, is not recommended for long-term treatment.

Patients taking lithium need to be monitored for polyuria and polydipsia. They also should have their electrolytes, blood urea nitrogen, creatinine, and lithium levels measured every 6 to 12 months. Patients with a history of lithium use should be evaluated for nephrogenic diabetes insipidus if they complain of polyuria and polydipsia. Symptomatic patients should have their serum sodium levels measured after 8 to 12 hours of water restriction and should be further evaluated if their sodium level is elevated. Hospitalized patients who have a current or remote history of lithium use need to monitored closely for hypernatremia. Lithium and nephrogenic diabetes insipidus should always be included in the differential diagnosis of a patient who has hypernatremia and an obscure medical history.

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