

Management and treatment of lithium-induced nephrogenic diabetes insipidus

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Lithium carbonate is a well documented cause of nephrogenic diabetes insipidus, with as many as 10 to 15% of patients taking lithium developing this condition. Clinicians have been well aware of lithium toxicity for many years; however, the treatment of this drug-induced condition has generally been remedied by discontinuation of the medication or a reduction in dose. For those patients unresponsive to traditional treatment measures, several pharmacotherapeutic regimens have been documented as being effective for the management of lithium-induced diabetes insipidus including hydrochlorothiazide, amiloride, indomethacin, desmopressin and correction of serum lithium levels.

Lithium carbonate is well known for its wide use in bipolar disorders due to its mood stabilizing properties. It is also employed in aggression disorders, post-traumatic stress disorders, conduct disorders and even as adjunctive therapy in depression. Lithium has many well documented adverse effects as well as a relatively narrow therapeutic range of 0.4 to 0.8 mmol/l. Clinically significant adverse effects include polyuria, muscle weakness, weight loss, ataxia, vertigo, seizures, incontinence of urine and feces, confusion and electrocardiographic changes.

Of major concern are lithium's adverse effects on the kidneys, specifically causing diabetes insipidus (DI) and a decreased glomerular filtration rate. Lithium-induced DI may occur in 10 to 15% of patients receiving lithium, especially those who have received long-term therapy (greater than 15 years) [1,2]. Given this potentially irreversible side effect, long-term therapy with lithium has been questioned, especially in elderly and renally impaired patients. The exact mechanism behind lithium-induced DI is not fully understood and a definitive treatment has never been outlined for practitioners. This review will cover the pathophysiology and diagnosis of lithium-induced DI as well as the different therapeutic treatment options available, including how to monitor, interpret and manage lithium levels.

Pathophysiology

Nephrogenic DI was first reported in 1892 [3]. In most cases of nephrogenic DI, solute excretion and renal filtration are normal but urine is hypotonic and there is a characteristic resistance to the antidiuretic effects of endogenous vasopressin. Congenital nephrogenic DI is typically

associated with a mutation(s) of vasopressin receptors. Acquired causes are tubulointerstitial disease (e.g., sickle cell disease, amyloidosis, obstructive uropathy), electrolyte disorders (e.g., hypokalemia and hypercalcemia), pregnancy, or conditions induced by a drug (e.g., lithium, demeclocycline, amphotericin B and vincristine) [3,4]. Lithium is the most common cause of drug-induced nephrogenic DI [5].

The development of nephrogenic DI following lithium administration likely involves multiple mechanisms. Abnormalities in the medullary osmotic gradient directed by antidiuretic hormone (ADH) or arginine vasopressin (AVP) and inhibition of the action of ADH on the renal tubules are both thought to be mechanisms by which lithium induces DI. The lack of response to ADH is due to the inhibition of adenylate cyclase and resultant decreased formation of cyclic cAMP [6]. cAMP serves as a second messenger to protein kinase A and the fusion of aquaporin storage vesicles to the luminal cell wall, which in turn allows the collecting ducts to become permeable and reabsorb water. Ultimately a patient with lithium-induced DI loses the ability to reabsorb water, in essence due to a loss of cAMP. Even after the administration of exogenous ADH, lithium has been shown to have continued effects, suggesting lithium has additional mechanisms by which it inhibits the ability to retain water [6]. This renal insensitivity to ADH may be dependent on the dosage as well as the duration of lithium therapy [7].

In addition to the development of DI, lithium also adversely affects the kidneys by inducing renal tubular acidosis, chronic interstitial nephritis and nephrotic syndrome. Lithium is filtered in the

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glomerulus and reabsorbed at several sites within the renal tubules and is also concentrated at the renal medulla. Due to the extensive nature by which lithium is processed by the kidneys, the possible renal adverse effects of lithium are logical. Polydipsia is reported in up to 40% of patients receiving lithium and polyuria in up to 20%; however, the severity of these adverse effects typically does not justify the cessation of therapy [5]. Progression to end-stage renal disease (ESRD) is rare and slowly progressive, representing only 0.22% of all ESRD cases and occurring after an average of 20 years of lithium therapy [8].

Diagnosis

A thorough physical examination and laboratory work up is essential to properly diagnose and determine the cause of nephrogenic DI. Patients with DI usually have a constellation of polyuria, urine osmolality below 200 mOsm/kg, and urine specific gravity less than 1.005. In patients who are not fluid restricted, serum osmolality usually remains within normal limits (280–290 mOsm/kg). Often laboratory values as well as other diagnostic tests are examined together [7,9].

Patients with DI who lack adequate water intake are at risk of developing a hyperosmotic state where serum sodium concentrations are elevated. Serum

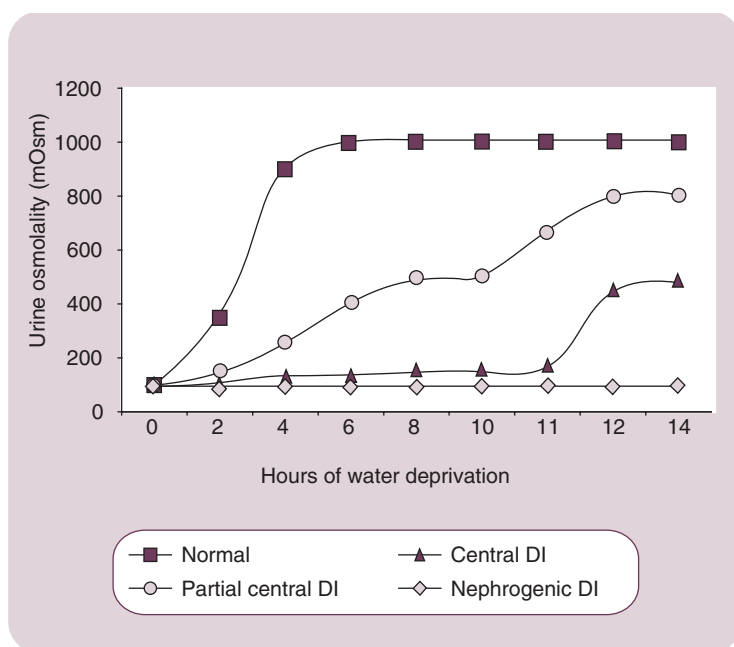
sodium concentrations, which in turn affect serum osmolality and water homeostasis, are under the control of thirst mechanisms, ADH and the kidneys [10]. Serum sodium concentrations are often used to determine a patient's water balance. Hypernatremia is a state in which the body's water stores are in deficit compared with sodium stores and is a common electrolyte abnormality whose cause is often unknown. Thus, using a serum sodium concentration alone is rather nonspecific in diagnosing DI. When interpreting serum sodium concentrations, there are several different categories into which a patient may be placed based on their signs, symptoms and fluid balance, in addition to the serum sodium concentration. In the case of nephrogenic DI, serum sodium concentrations will be elevated. In these patients, there will be absolute free water loss as opposed to other syndromes that may be causing hypotonic fluid loss.

A water deprivation test is helpful in diagnosing DI and allows for the differentiation between nephrogenic versus central DI. [9,11,12]. Differing responses to water deprivation tests due to different abnormalities in water homeostasis can be seen in Figure 1. To determine whether the DI is of nephrogenic origin, a single five-unit dose of subcutaneous desmopressin may be administered after the patient has been deprived of water for at least 4 to 18 hours. Adequate water deprivation is noted by a weight loss of 3 to 5 lbs or two consecutive urine osmolality values, checked hourly, that differ by less than 30 mOsm/kg [9,12]. A final measure of urine osmolality is obtained 1 h after administration of the desmopressin. In lithium-induced nephrogenic DI, the urine often remains dilute with lower urine osmolality levels of less than 200 mmol/l, even after administration of exogenous AVP. When the cause is central DI, urine osmolality should typically increase in correlation with a decrease in urine output, serum sodium concentrations and serum osmolality [5,9,11]. Urine output in nephrogenic DI can reach 10 to 18 l/day in severe cases and 3 to 6 l/day in milder cases. Plasma osmolality is typically greater than 290 mOsmol/kg in patients who have been placed in fluid restriction [11]. Finally, in nephrogenic DI, arginine vasopressin levels are often normal or elevated. Refer to Table 1 for a review of common laboratory abnormalities observed with nephrogenic DI.

Signs & symptoms

The complications observed in patients with lithium-induced DI are subsequent to the development of dehydration and hypernatremia. In

Figure 1. Response to exogenous administration of arginine vasopressin in different types of diabetes insipidus [11].



Adapted with kind permission from *Cecil's textbook of Medicine, 19th Edition*, Dennis VW (Ed). WB Saunders Publishers, PA, USA, 495, (1992).

Table 1. Laboratory abnormalities.

Laboratory	Normal	Abnormality seen in nephrogenic diabetes insipidus
Urine osmolality	1000 mmol/l	<100 mmol/l
Urine output	<3 l/day	>3 l/day up to 18 l/day
Plasma osmolality	275–290 mOsmol/kg	>290 mOsmol/kg
Arginine vasopressin level	0.9–4.6 pmol/l	>4.6 pmol/l
Administration of exogenous arginine vasopressin		Little to no rise in urine osmolality

most cases, findings of DI on physical examination are most related to CNS dysfunctions secondary to severe changes in serum sodium concentrations. In most outpatient cases of DI, patients are either very young or elderly. In a majority of the reported cases of lithium-induced DI, the patients were elderly and had received lithium for chronic long-term therapy [13–15]. As hypernatremia is an abnormality likely to occur in the elderly, the safety of long-term therapy with lithium in the elderly has been questioned. In younger infantile patients, common signs and symptoms of hypernatremia are hyperpnea, muscle weakness, insomnia, observed in cases of acute sodium loading and aggressive rehydration. Elderly patients are often asymptomatic until sodium serum concentrations reach 160 mmol/l [10]. They may also experience intense thirst, decreased consciousness, muscle weakness, confusion and coma. In the inpatient setting, hypernatremia affects patients of all ages and the signs and symptoms may be harder to detect due to pre-existing neurologic dysfunctions. Patients with nephrogenic DI usually intake adequate amounts of water but may develop hypernatremia when fluid intake is restricted for any reason [13]. While lethargy, coma and brain shrinkage is common, dural sinus thrombosis has been reported in at least one case as a complication of hypernatremia secondary to long-term lithium use. In this particular case, the thrombosis was hemorrhagic and fatal [13]. In the management of chronic hypernatremia, it is important to slowly reduce serum sodium concentrations to prevent cerebral edema and convulsions. In the case of lithium-induced DI, these patients will have experienced prolonged hypernatremia and therefore should be treated with a more conservative method to prevent further neurologic complications. Morbidity and mortality from hypernatremia itself is

difficult to define given the number of other comorbidities that are often present in patients who experience symptomatic hypernatremia. Often the complications that arise from hypernatremia are not due to the syndrome itself, but rather the inappropriate treatment.

Treatment

As with most drug-induced conditions that are fully or partially reversible, general treatment of lithium-induced DI should begin with the discontinuation of lithium therapy. However, in many patients, this may not always be feasible [16]. Even when the drug can be discontinued, lithium-induced DI may take several weeks to correct and may not ever completely resolve [17,18]. Over 25% of patients who develop polyuria while taking lithium will have a diminished ability to concentrate their urine 1 year after stopping lithium [12].

Fluid restriction to reduce urine volume is not recommended in lithium-induced DI as it may lead to extreme hypernatremia and the potential for hypertonic encephalopathy [12]. It is important to note that the diagnosis and differentiation of DI typically involves a water deprivation test. In the case of lithium-induced DI, it may serve to detect a mixed picture where lithium-induced nephrogenic DI co-exists with either primary polydipsia or central DI. However, aside from the water deprivation test for diagnostic purposes, fluid restriction in lithium-induced DI is dangerous and should be avoided.

If concurrent hypercalcemia and/or hypokalemia are present along with lithium-induced DI, these factors must also be corrected [19]. Either of these states may cause significant ADH resistance and reduced aquaporin-2 expression, leading to increased urinary water excretion and loss of concentrating ability [3]. Once all of the correctable contributing factors are resolved, treatment with pharmacologic agents may be required. Amiloride, thiazide diuretics, indomethacin and desmopressin have all been used to successfully treat lithium-induced DI.

As mentioned previously, correction of hypernatremia associated with lithium-induced DI must be carried out slowly in order to avoid further worsening of the neurologic status. Although a thorough discussion of the treatment of hypernatremia is beyond the scope of this article, a common error in the overall management of the disease is the use of isotonic saline, which will not lower serum sodium concentrations effectively. Conversely, aggressive lowering of serum sodium by more than

0.5 mEq/h is detrimental and will increase the risk of cerebral edema [10]. Administration of fluids and additional agents should be guided by frequent monitoring of laboratory values as well as hydration status; however, if urine output exceeds 4 l/day, additional therapies may be needed [14].

Amiloride

Multiple authors suggest that the potassium-sparing diuretic, amiloride, in doses of 5 to 20 mg daily, should be considered first-line therapy for the management of lithium-induced DI [9,20–23]. Lithium is thought to inhibit vasopressin-mediated opening of aquaporins and aquaporin expression in the collecting ducts. Amiloride blocks the cellular uptake of lithium from the distal tubules and collecting ducts [21]. By preventing lithium from entering these cells, amiloride blunts lithium's inhibition of water reabsorption and ultimately decreases urine output [7]. Due to this direct mechanism, improvement in symptoms can often be seen even in patients who cannot discontinue lithium therapy [21]. Some authors postulate that if amiloride directly blocks lithium uptake into aquaporin-expressing tubular cells, then administering amiloride from the start of lithium therapy could theoretically prevent lithium-induced DI [7]. The clinical utility of this theory has never been studied to our knowledge.

The use of amiloride in lithium-induced DI has multiple advantages over alternative therapies. Due to its mechanism of action, amiloride may be a safer choice than thiazides or nonsteroidal anti-inflammatory drugs (NSAIDs) as it is less likely to increase serum-lithium concentrations to toxic levels [23]. Secondly, amiloride use will not contribute to the development of hypokalemia due to its potassium-sparing effects [9]. This obviates the need for potassium supplementation, which is usually required when treating lithium-induced DI with thiazides.

Thiazides

The use of thiazide diuretics to treat DI has been documented since 1959 in animal models and as early as 1961 in humans [24,25]. The use of thiazides in conjunction with a sodium-restricted diet of less than 2 g/day has been shown to decrease urine volume by 40 to 50% [17,19]. The paradoxical effect of using thiazide diuretics to treat lithium-induced DI has been studied extensively and multiple hypotheses regarding the mechanisms behind their beneficial effects have been described.

Currently, the most well established mechanism to explain the efficacy of thiazides in lithium-induced DI relates to extracellular volume contraction. Initially, thiazides reduce sodium reabsorption in the distal tubule and increase urinary sodium excretion [16]. This reduction in sodium reabsorption causes extracellular fluid volume contraction and a reduction in glomerular filtration rate. Sodium and water reabsorption increase at the proximal tubule, which diminishes dilute urine formation at distal sites and decreases urine volume [16,20].

Some authors believe that thiazide-mediated inhibition of sodium reabsorption in the distal tubule cannot be solely responsible for the anti-diuretic effect of thiazide agents [26–28]. In addition to the extracellular volume contraction, thiazides may redistribute total body sodium and increase papillary osmolality [27]. It has also been postulated that thiazides can increase water permeability in the collecting duct and enhance water reabsorption [28]. In a recent study, rats with lithium-induced DI that were treated with hydrochlorothiazide for 7 days were shown to have significantly increased aquaporin expression and significantly decreased urine volume compared with nontreated controls [26]. This suggests the possibility that thiazides may directly increase water permeability in the collecting duct via increased aquaporin expression.

Unfortunately, the volume contraction induced by thiazides results in decreased lithium excretion and the potential for lithium toxicity [20]. Similar to sodium and water, lithium is also reabsorbed in the proximal tubules. Any treatment modality that increases the absorption of sodium in the proximal tubule will cause a concurrent increase in lithium reabsorption [7]. When lithium-induced DI is treated with thiazide diuretics, lithium levels may rise by 25–40% [26,29]. Additionally, thiazides can cause hypokalemia that may not fully respond to the administration of potassium chloride [16]. Due to this potential complication, close monitoring of potassium levels is necessary during thiazide treatment and potassium supplementation is often required. The addition of amiloride to thiazide therapy has an additive effect on urine volume reduction while lessening the chances for thiazide induced hypokalemia and alkalosis [30].

Indomethacin

Indomethacin, in doses of 100 to 150 mg daily has been cited extensively as having beneficial effects in nephrogenic DI and may be a

useful adjunct in therapy due to potentiation of ADH activity [23,31,32]. In the kidneys, adenylyl cyclase production and subsequent opening of aquaporins is stimulated by vasopressin. Prostaglandin E2 inhibits adenylyl cyclase, which diminishes vasopressin-induced water permeability in the collecting ducts and causes water to be excreted in the urine rather than reabsorbed [16]. Indomethacin blocks prostaglandin E2 activity and causes increased water reabsorption in the collecting ducts [20].

Additionally, indomethacin has been shown to increase sodium reabsorption in the thick ascending loop of Henle, which causes more water to be reabsorbed rather than excreted in the urine [7]. However, this effect also leads to increased lithium reabsorption in the loop of Henle, and may precipitate lithium toxicity [23]. In a trial carried out by Frolich and colleagues [33], lithium levels increased by 59% in psychiatric patients and 30% in healthy volunteers who received 50 mg of indomethacin three-times daily. Indomethacin may also severely disrupt kidney perfusion pressure and lead to acute renal failure, especially in the elderly [7]. Owing to these negative effects, indomethacin should not be considered as first-line therapy for lithium-induced DI.

Desmopressin

By definition, nephrogenic DI is characterized by normal plasma ADH levels and an inadequate response to ADH in the kidneys. Therefore, it would be expected that exogenous administration of desmopressin would be of little use in lithium-induced nephrogenic DI. However, in one article, the authors suggest that the use of a thiazide, indomethacin, and desmopressin in combination, may decrease urine output by up to 80% [17]. In addition, in another case report, the administration of large doses of desmopressin in patients with lithium-induced DI was associated with decreased polyuria [34]. The addition of desmopressin to a treatment regimen can be useful in some patients with lithium-induced DI as they may have a combination of lithium-induced nephrogenic DI along with central DI from another cause that is responsive to desmopressin. There is also some evidence that desmopressin, but not endogenous vasopressin, can partially reverse the lithium-induced decrease in aquaporin expression in the collecting ducts [20,35].

Management of lithium levels

Of the many case reports involving lithium-induced DI, not all cases demonstrated elevated levels of lithium (normal 0.4–0.8 mmol/l). While

Table 2. Drug therapy for lithium-induced diabetes insipidus.

Treatment	Dose	Comments	Ref.
Amiloride	5–20 mg daily; may be divided b.i.d	First line for lithium-induced DI; directly blocks Li ⁺ uptake in kidney; less likely to increase Li ⁺ levels; possible hyperkalemia with use	[8,20–23]
Hydrochlorothiazide*	50–150 mg daily; may be divided b.i.d/t.i.d	Longest and most widely used agent in literature; multiple MOA's; increase Li ⁺ levels; possible hypokalemia with use	[24–26,29]
Indomethacin	100–150 mg daily; divide b.i.d/t.i.d [#]	Consider use as adjunct, not 1st line therapy; may potentiate ADH activity; increase Li ⁺ levels; potential for ARF, especially in elderly	[23,31–33]
Desmopressin	10–40 µg intranasal daily; may divide b.i.d/t.i.d OR 2–4 µg s.c/iv. daily; divide b.i.d [¶]	Little data to support use in Li ⁺ induced DI; may be useful in mixed Li ⁺ induced DI with central DI component	[17,20,33, 35]

*Any thiazide diuretic may be substituted in equivalent doses.

[#]Other NSAIDs have been used, but most of the literature describes indomethacin use

[¶]Doses used in treatment of central DI; no specific data for dosage in lithium-induced DI

ADH: Anti-diuretic hormone; ARF: Acute renal failure; b.i.d: Twice daily; iv.: intravenously; MOA: Mechanism of action; s.c.: Subcutaneously; t.i.d: Three times a day.

it has been suggested that these laboratories should be monitored annually, more frequent monitoring may be prudent in elderly patients as well as in those patients who will receive lithium long term. In a retrospective case review of 149 patients who received lithium long term, a decreased glomerular-filtration rate was associated with the duration of lithium treatment and increased age [36]. In this study, patients who were on lithium for a longer period of time were twice as likely to experience decreased urine-concentrating capacity as well as decreased glomerular filtration rate. In a case report of two patients with lithium-induced DI, 8 years and were also over the age of 65 years [14]. Only one of these patients had an elevated level of lithium. Of patients on lithium, approximately 20% are over the age of 65 years. Given the association of lithium-induced DI with age and length of therapy but not lithium level, patients should be thoroughly educated about staying well-hydrated in addition to frequent monitoring of urine output and renal function. Institutionalized patients, who may or may not be able to let others know when they are thirsty and need fluids, should be monitored very carefully and kept adequately hydrated.

Finally, targeting a therapeutic range of 0.4 to 0.8 mmol/l is suggested; however, DI can still occur within these therapeutic levels.

Expert commentary

In lithium-induced DI, underlying factors contributing to the condition should be resolved before any specific therapies are introduced. This includes discontinuation of lithium therapy when possible and correction of electrolyte imbalances such as hypernatremia, hypercalcemia and hypokalemia, if present. In patients who continue to take lithium, it is recommended that trough levels less than 1 mmol/l be maintained along with attempting to maintain urinary output at less than 4 l/day [7,8]. Dietary sodium restriction of less than 2 g daily is necessary for the maintenance of the mild extracellular volume contraction required for the antidiuretic effect of thiazides [20]. Treatment regimens (Table 2) involving amiloride or thiazides alone or in combination with each other +/- indomethacin have all been shown to be successful in the treatment of lithium-induced DI and its symptoms. In certain patients with lithium-induced DI and an additional component of central DI, the addition of desmopressin may also be useful.

Highlights

- Lithium is the most common cause of nephrogenic diabetes insipidus (DI), which may occur in 10–15% of patient taking the medication.
- Polydipsia and polyuria develop in up to 40 and 20% of patients, respectively.
- The development of DI may be dependent on the dosage as well as the duration of lithium therapy.
- Lithium promotes a lack of response to ADH through inhibition of cAMP formation which results in patients losing the ability to reabsorb water and polyuria.
- Treatment regimens involving amiloride or thiazides alone or in combination with each other +/- indomethacin have all been shown to be successful in the treatment of lithium-induced DI and its symptoms.
- Desmopressin alone may be of little use.
- Target therapeutic range for lithium is 0.4 to 0.8 mmol/l; however, DI can still occur within these levels.

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