

# Drug-Induced Diabetes Insipidus

## Incidence, Prevention and Management

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### Abstract

Drug-induced diabetes insipidus is always of the nephrogenic type, i.e. unresponsiveness of the kidneys to the action of antidiuretic hormone. This condition is easily diagnosed by measuring urinary concentrating capacity during a thirst test (e.g. 12 hours of water deprivation) or by administration of a modified antidiuretic hormone, desmopressin, to demonstrate the renal unresponsiveness. Drug-induced nephrogenic diabetes insipidus is not a common disorder except in patients receiving treatment with lithium salts for affective disorders where it may affect about 10% of patients treated long term (15 years). Drug-induced nephrogenic diabetes insipidus caused by other drugs usually occurs in critically ill patients in intensive care units receiving a multitude of drugs dominated by antimicrobials and cytostatics. A search of the World Health Organization's adverse effect database revealed 359 reports of drug-induced diabetes insipidus. Lithium was the most common cause (159 reports) followed by foscarnet (15) and clozapine (10).

Treatment is symptomatic in most patients and the offending drug should be stopped. If urine volumes exceed 4 L/day, treatment with thiazides and amiloride has been advocated, and nonsteroidal anti-inflammatory drugs, such as indomethacin, may be tried in severe cases. Prevention of lithium-induced nephrogenic diabetes insipidus is an important aspect of the treatment of affective disorders.

In patients treated long term it appears to be only partly reversible upon lithium discontinuation. Close monitoring of the treatment aiming at 12-hour trough value of 0.4 to 0.6 mmol/L is recommended. Yearly measurement of the urinary volume/day is effective in making both the patient and the physician aware of the development of the drug-induced nephrogenic diabetes insipidus. The condition is a serious adverse effect because of the risk of developing dehydration and aggravation of drug intoxications.

Diabetes insipidus is caused by a failure to concentrate urine due to a deficiency in the action of the antidiuretic hormone vasopressin. Diabetes insipidus appears in two forms: neurogenic (central) and nephrogenic (peripheral). The neurogenic forms of diabetes insipidus are caused by insufficient, incomplete or complete lack of secretion of the antidiuretic hormone, while the nephrogenic forms are caused by unresponsiveness of the kidneys to the action of antidiuretic hormone.

Both neurogenic and nephrogenic forms may be familial or acquired.<sup>[1]</sup> The neurogenic acquired forms are mostly neoplastic, traumatic ischaemic and or infectious in nature, that is, conditions that destroy the pituitary or the neural connections of the pituitary to the hypothalamus; these forms of diabetes insipidus are not drug induced. Drug-induced diabetes insipidus is always of the nephrogenic type. There are also other causes of acquired nephrogenic diabetes insipidus such as metabolic disorders resulting in hypokalaemia and hypercalcaemia and renal diseases such as polycystic kidney disease and obstructive uropathy. Chronic pyelonephritis, specifically analgesic nephropathy, with structural destruction of the distal parts of the nephron, presents with similar symptoms and signs as nephrogenic diabetes insipidus. Valuable reviews of diabetes insipidus have been published by several authors.<sup>[2-4]</sup>

This review concentrates on drug-induced nephrogenic diabetes insipidus with a focus on lithium. This is an area of great concern in several specialities such as nephrology, endocrinology, intensive care units and psychiatry.

## 1. General Aspects of Nephrogenic Diabetes Insipidus

### 1.1 Pathophysiology

Water excretion is controlled by a number of mechanisms. Recently, the aquaporins (water transport channels) have been described (for a review see Nielsen et al.<sup>[5]</sup>). The water channels of the collecting ducts of the nephron which are responsible for the urinary concentrating mechanisms are of the aquaporin-2-type. They are sensitive to the action of antidiuretic hormone. If the aquaporins are blocked, destroyed or otherwise unresponsive to antidiuretic hormone, the collecting duct then becomes impermeable to water and the syndrome of nephrogenic diabetes insipidus will result.

Nephrogenic diabetes insipidus is defined as the failure to concentrate urine despite adequate secretion of antidiuretic hormone. The diagnosis can be easily made by measuring urinary concentrating capacity during a thirst test (e.g. 12 hours of water deprivation) or by measuring circulating vasopressin levels or by administration of a modified antidiuretic hormone, desmopressin (desamino-D-arg-vasopressin) to demonstrate renal unresponsiveness to antidiuretic hormone. Nephrogenic diabetes insipidus is characterised by polyuria which is often severe and causes thirst and polydipsia. Polyuria may be quite marked and often amounting to more than 4 to 6 L/day with a real risk of developing dehydration and accompanying complications. Nephrogenic diabetes insipidus must be considered a serious drug-induced condition.

## 1.2 Incidence

A number of drugs have been shown to cause nephrogenic diabetes insipidus. During the 1990s many case reports have described this disorder and these are listed in table I (based on a Medline search). However, the commonest drugs to cause nephrogenic diabetes insipidus, are lithium salts and these agents will therefore be discussed separately.

Drug-induced nephrogenic diabetes insipidus is not very common condition except in patients receiving lithium. It usually appears in critically ill patients and it is most often diagnosed in the intensive care unit. As shown in table I, this condition can be caused by a very varied group of drugs which is dominated by antimicrobials and cytostatics. In literature published prior to 1990, several other drugs were also implicated in causing nephrogenic diabetes insipidus, such as demeclocycline, methoxyflurane, colchicine, vinca alkaloids, gentamicin, isophosphamide and glibenclamide (glyburide).<sup>[2]</sup>

A recent search of the World Health Organization's adverse effects database revealed a total of 385 reports of drug-induced diabetes insipidus. Among the numerous drugs implicated, lithium was the single most common cause, accounting for 159 of the reports. The next most common cause was foscarnet with 15 reports, followed by clozapine with 10 reports.

## 1.3 Prevention and Management

Prevention of drug-induced nephrogenic diabetes insipidus is difficult because this adverse effect often occurs in critically ill patients and in difficult treatment conditions. A specific discussion of measures that can be taken to prevent lithium-induced nephrogenic diabetes insipidus is given in section 2.6.

The following guidelines are usually recommended for the management of nephrogenic diabetes insipidus. Milder forms of the condition need no special treatment apart from controlling water intake. Patients with urine volumes of about 3 to 4

**Table I.** Drugs implicated as causing nephrogenic diabetes insipidus case reports (1990-1997)<sup>a</sup>

| Drug             | References |
|------------------|------------|
| Foscarnet        | 6-10       |
| Cidofovir        | 11         |
| Amphotericin     | 12, 13     |
| Fluvoxamine      | 14         |
| Cyclophosphamide | 15         |
| Cimetidine       | 16         |
| Lobenzarit       | 17, 18     |
| Epirubicin       | 19         |
| Antipsychotics   | 20, 21     |
| Verapamil        | 22         |

<sup>a</sup> Lithium salts not included.

L/day can be considered to have a mild form of the condition.

Patients with more serious forms of polyuria, i.e. urine volume of more than 4 L/day, may require treatment with diuretics such as thiazides and amiloride. However, thiazide treatment may be counterproductive due to the induction of hypokalaemia which in turn may accentuate the nephrogenic diabetes insipidus. The mechanism of action of amiloride is believed to be the prevention of the entrance of lithium into the cells of the distal tubule while chlorothiazide acts via an increase in proximal sodium reabsorption secondary to increased urinary sodium excretion. The increase in proximal sodium reabsorption runs in parallel with an increased lithium reabsorption.

Nonsteroidal anti-inflammatory drugs (NSAIDs), for example indomethacin, are often used in intensive care units for treating nephrogenic diabetes insipidus. Their effects on water excretion are due to the following mechanisms: (i) blocking of the metabolism of cyclic adenosine monophosphate due to inhibition of phosphodiesterases and; (ii) increasing the sodium reabsorption in the medullary thick ascending loop of Henle. The tonicity and solute reabsorption of the medullary part of the nephron are enhanced by NSAIDs. On the other hand, NSAIDs may have negative effects on kidney perfusion and glomerular filtration especially in critically ill patients. NSAID treatment should

not be considered 'standard treatment' of nephrogenic diabetes insipidus.

## 2. Lithium and Nephrogenic Diabetes Insipidus

Lithium was discovered by the Swedish chemist Arfwedson in 1817, and it was introduced into medical use during the second half of the nineteenth century. However, its use was subsequently abandoned because of toxic complications. Lithium was reintroduced into psychiatry in 1949 for the treatment of mania.<sup>[23]</sup> Its prophylactic effect was discovered and confirmed in the late 1960s<sup>[24-26]</sup> and since then lithium has been in widespread use in the treatment of affective disorders.

The toxicity of lithium and its narrow therapeutic window became evident early on to investigators, as did the relationship between a low-sodium diet and the development of lithium intoxication in humans.<sup>[27]</sup> Sodium conservation was found to stimulate lithium reabsorption and increase the intrarenal concentration of lithium.

Lithium-induced nephrogenic diabetes insipidus is not a drug reaction but a consequence of one of the many biological effects of lithium. It is dose dependent and even small doses may cause nephrogenic diabetes insipidus. However, it is often also claimed that lithium has a central action which causes thirst and a primary polydipsia and a secondary inhibition of antidiuretic hormone release.

### 2.1 Early Findings and Views on Lithium-Induced Polyuria

In an early review of lithium, reversibility of polyuria was observed and it was also found that lithium could decrease urinary concentrating capacity at therapeutic doses.<sup>[28]</sup> These conclusions were supported by case reports<sup>[29,30]</sup> and discussed by Forrest et al.<sup>[31]</sup>

The possibility of irreversible kidney damage as a consequence of lithium therapy was suggested in 1972 by Evan and Ollerich<sup>[32]</sup> in rat studies, and Lindop and Padfield<sup>[33]</sup> made similar observations in a case report including post mortem microscop-

ical examination of the kidneys. The histopathological findings in humans were confined to the distal parts of the nephron. However, it was not until Hestbech et al.<sup>[34]</sup> had published the landmark study on lithium-induced chronic damage both to the tubules and glomeruli that the concept of lithium nephropathy evolved. Tubular water-conserving ability was more or less lost while severe glomerular insufficiency or terminal uraemia was considered an unlikely event.<sup>[35]</sup>

The question of lithium-induced chronic renal insufficiency is beyond the scope of this review, but it may be mentioned that in spite of 20 years of renal function studies and case reports only a few cases of uraemia ascribed to lithium have been published<sup>[36,37]</sup> indicating that the incidence of uraemia with lithium is actually very low.

### 2.2 Lithium Interference with Physiological Water Transport

Lithium is freely filtered through the glomerulus, and is reabsorbed in the proximal tubules concomitant with sodium and water. Whether any net absorption takes place in the more distal parts of the nephron is still an unanswered question. The reabsorption of water in the distal tubules causes an increase in intraluminal lithium concentration to a maximum which at the papillary tip may reach 40 times the serum lithium concentration.<sup>[38,39]</sup> The intracellular lithium concentration is, however, not known.

The mechanism by which lithium causes reversible nephrogenic diabetes insipidus is thought to be an inhibition, at the level of the duct cell membrane, of the 'opening' of aquaporins by vasopressin via complex mechanisms including activation of adenylyl cyclase and production of cyclic adenosine monophosphate.<sup>[4,39]</sup> Presumably, lithium antagonises these processes. When polyuric lithium patients were given amiloride, a diuretic which prevents lithium from entering the cell, polyuria diminished and osmolality increased.<sup>[40]</sup>

In rats, Christensen<sup>[41]</sup> found that desmopressin but not vasopressin caused a partial reversal of lithium-induced diabetes insipidus. This difference in

the effect of the 2 antidiuretic substances may be related to the observation that desmopressin but not vasopressin causes a marked increase in apical plasma membrane aquaporin type 2 expression in the collecting duct cells.<sup>[39]</sup> Hypercalcaemia and primary hyperparathyroidism may be aetiological contributing factors for lithium-induced nephrogenic diabetes insipidus.<sup>[42]</sup>

The mechanism by which lithium causes an irreversible nephrogenic diabetes insipidus is not known. However, the low oxygen tension in the papillary medulla renders the cells particularly vulnerable to any kind of damage because of the increased oxygen demand during repair processes. Hypothetically, the intracellular lithium concentration may reach a certain critical level before permanent damage will result. Unfortunately, the lithium concentration inside the distal tubular cells has not been measured so far.

### 2.3 The Prevalence of Lithium-Induced Nephrogenic Diabetes Insipidus

In a review of lithium-induced renal adverse effects the prevalence of nephrogenic diabetes insipidus was estimated to vary between 15 and 87%.<sup>[43]</sup> However, there was a considerable variation in the reference values used and especially in the kind of methods used for the determination of maximal concentrating capacity. We found that among 142 patients who had been receiving lithium for 15 years or more, 15 patients (12%) had nephrogenic diabetes insipidus as diagnosed with the desmopressin method.<sup>[44]</sup>

### 2.4 The Clinical Importance of Lithium-Induced Nephrogenic Diabetes Insipidus

Polyuria *per se* is not harmful, but may be quite troublesome for the patient. However, the increased risk of dehydration and of lithium intoxication secondary to dehydration makes it a potentially lethal complication. To our knowledge, however, only 3 cases of a lethal outcome have been published. These patients were all dehydrated

for different reasons: adherence to a religious fast; a prolonged period of restraint with insufficient supply of water and; dehydration after surgery. Numerous reports on milder forms have been published and have recently been reviewed.<sup>[45]</sup>

### 2.5 The Treatment of Lithium-Induced Nephrogenic Diabetes Insipidus

Because of the importance of serum lithium concentration in causing nephrogenic diabetes insipidus,<sup>[46]</sup> a dose reduction may suffice in the case of reversible lithium-induced nephrogenic diabetes insipidus. A further dose reduction may be possible by combining lithium with an anticonvulsant<sup>[47]</sup> such as carbamazepine<sup>[48,49]</sup> or valproic acid (sodium valproate).<sup>[50]</sup>

The complete replacement of lithium for an anticonvulsant would be the next reasonable step. When these counter-measures are not feasible or effective, treatment with the diuretics amiloride and chlorothiazide should be tried alone or in combination. Indomethacin has also been used.<sup>[51]</sup>

The ability of indomethacin to reduce polyuria may also be a consequence of sodium losses. Prostaglandin synthesis inhibition is a less likely mechanism of action since not all NSAIDs share the ability to reduce polyuria. It should be observed, however, that indomethacin-like chlorothiazides and amiloride cause an increase of serum lithium concentration because of a reduction in lithium clearance.

### 2.6 Prevention of Lithium-Induced Nephrogenic Diabetes Insipidus

The first rule is to use the lowest possible lithium dose. Lithium treatment should be monitored using the 12-hour trough value and serum concentrations in the range of 0.4 to 0.6 mmol/L are usually considered acceptable. Serum concentrations above 1.0 mmol/L should definitely be avoided.

Regular measurement of urinary volume will make both the patient and the physician aware of the presence of the polyuria and its severity. Patients are often so adapted to their condition that

they consider urinary volume up to 4 L/day as quite normal. A switch to an alternative treatment should be considered when urinary volumes exceed this value.

It may not always be possible to prevent the development of lithium-induced nephrogenic diabetes insipidus. The likelihood of developing reduced urinary concentrating capacity increases with lithium treatment time. Among patients who have received lithium for a limited time, nephrogenic diabetes insipidus is rare. The risk of reduced urinary concentrating capacity is also associated with a severe and treatment-resistant type of affective disorder, necessitating polypharmacy and frequent use of in-patient treatment.<sup>[44]</sup>

If amiloride prevents the entrance of lithium into the cells, it should theoretically be possible to avoid toxic intracellular lithium concentrations by giving amiloride from the very beginning of the lithium treatment. Since many patients discontinue lithium treatment within a few years, and since many of those who continue will never develop nephrogenic diabetes insipidus, the general use of long term preventive amiloride treatment is not recommended. However, in patients who develop a progressive polyuria, and particularly in those who are at high risk for lithium-induced nephrogenic diabetes insipidus, amiloride treatment should be considered.<sup>[44]</sup>

#### 2.7 How to Prevent Fatal Consequences of Lithium-Induced Nephrogenic Diabetes Insipidus

Several precautions should be taken to avoid the possible serious consequences of lithium-induced nephrogenic diabetes insipidus. Among such measures are yearly measurements of urinary output. Furthermore patients should be taught about water and electrolyte balance and explained how lithium is processed in the cells and excreted. The causes and the signs and symptoms of lithium intoxication should be discussed with the patients and these discussions should be repeated at regular intervals. Patients should carry a card indicating that they are receiving lithium treatment.

Lastly, but not least, psychiatrists, internists, surgeons and anaesthesiologists should be taught about the existence and hazards of lithium-induced nephrogenic diabetes insipidus and how to prevent the serious adverse effects of lithium treatment.

### 3. Conclusions

Drug-induced diabetes insipidus is most often caused by lithium salts that are used for treatment of affective disorders. Several other classes of drugs such as antibacterials and cytostatics may also cause this condition. These drugs render the kidney unresponsive to antidiuretic hormone by interfering with the aquaporin-type-2 water channels in the collecting ducts. The condition is easily diagnosed using thirst tests during simultaneous measurement of plasma antidiuretic hormone or administration of desmopressin, a synthetic antidiuretic hormone.

The condition must be considered as a serious adverse effect, because the possibility of dehydration and aggravation of drug intoxication, especially lithium, are obvious risks. Treatment should focus on eliminating the offending drugs, controlling salt and water balance and in severe cases attempting to reduce urinary output using treatment with chlorothiazide, amiloride or prostaglandin synthetase inhibitors, e.g. indomethacin.

The best way to reduce the risks of lithium is to keep patients well informed about the condition of nephrogenic diabetes insipidus.

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