

## Lithium nephrotoxicity revisited

Jean-Pierre Grünfeld and Bernard C. Rossier

**Abstract** | Lithium is widely used to treat bipolar disorder. Nephrogenic diabetes insipidus (NDI) is the most common adverse effect of lithium and occurs in up to 40% of patients. Renal lithium toxicity is characterized by increased water and sodium diuresis, which can result in mild dehydration, hyperchloremic metabolic acidosis and renal tubular acidosis. The concentrating defect and natriuretic effect develop within weeks of lithium initiation. After years of lithium exposure, full-blown nephropathy can develop, which is characterized by decreased glomerular filtration rate and chronic kidney disease. Here, we review the clinical and experimental evidence that the principal cell of the collecting duct is the primary target for the nephrotoxic effects of lithium, and that these effects are characterized by dysregulation of aquaporin 2. This dysregulation is believed to occur as a result of the accumulation of cytotoxic concentrations of lithium, which enters via the epithelial sodium channel (ENaC) on the apical membrane and leads to the inhibition of signaling pathways that involve glycogen synthase kinase type 3 $\beta$ . Experimental and clinical evidence demonstrates the efficacy of the ENaC inhibitor amiloride for the treatment of lithium-induced NDI; however, whether this agent can prevent the long-term adverse effects of lithium is not yet known.

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#### Learning objectives

Upon completion of this activity, participants should be able to:

- 1 List indications for the use of lithium in psychiatry.
- 2 Describe the prevalence and types of nephrogenic adverse effects of lithium.
- 3 Identify the histologic and radiologic features of lithium nephrotoxicity.
- 4 Describe the risk of developing end-stage renal disease with lithium nephrotoxicity.
- 5 Describe the American Psychiatric Association guidelines for screening for lithium nephrotoxicity.

### Introduction

Lithium salts were first used as table salt substitutes in patients with hypertension or congestive heart failure,

#### Competing interests

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although the FDA withdrew them from the market in 1949 following the occurrence of acute, lethal, lithium intoxications. In the same year, however, the value of lithium in the treatment of acute mania was recognized. Subsequently, a controlled trial demonstrated the efficacy of lithium in the prevention of both suicide and recurrence of bipolar disorder, a frequent (approximate prevalence 1% worldwide) and devastating disease in which major depressive episodes alternate with manic episodes.<sup>1,2</sup> Lithium therapy became increasingly widespread in the 1970s, and its use was extended to bipolar spectrum disorders and refractory unipolar major depression, the lifetime prevalence of which disorders could be as high as 5% of the US population.<sup>3</sup> The use of lithium therapy might be broadened even further in the future. Lithium has been shown in mice and in humans to delay the progression of amyotrophic lateral sclerosis, a devastating neurodegenerative disorder that currently has no effective treatment.<sup>4</sup> Lithium might also be of use in the treatment of Alzheimer disease.<sup>5</sup>

As a monovalent cation, lithium is freely filtered through the glomeruli, and up to 80% of the filtered load is reabsorbed, mostly in the renal proximal tubule. A small fraction is reabsorbed in distal parts of the nephron through the epithelial sodium channel (ENaC). As a result, serum concentrations of this ion increase in lithium-treated patients when the glomerular filtration rate (GFR) is decreased by chronic kidney disease (CKD), hypovolemia, use of NSAIDs, or exposure to renin–angiotensin system inhibitors, or when proximal tubular reabsorption is stimulated by reduced salt intake or use of diuretics.<sup>3</sup>

The nephrotoxic effects of lithium are characterized by reduced urinary concentrating capacity (which can be

Department of Nephrology, Necker Hospital, Université Paris Descartes, Paris, France (J-P Grünfeld). Department of Pharmacology and Toxicology, Université de Lausanne, Lausanne, Switzerland (BC Rossier).

Correspondence: J-P Grünfeld, Hôpital Necker, 161 Rue de Sèvres, 75743 Paris, Cedex 15, France [jean-pierre.grunfeld@nck.ap-hop-paris.fr](mailto:jean-pierre.grunfeld@nck.ap-hop-paris.fr)

detected as early as 8 weeks after lithium initiation)<sup>6</sup> and CKD (which usually occurs after 10–20 years or more of lithium administration).<sup>7,8</sup> Hypercalcemia is another long-term sequela of chronic lithium treatment. This Review describes the presentation, pathophysiology and treatment of these toxic renal effects.

### Lithium-induced tubular dysfunction

Nephrogenic diabetes insipidus (NDI) is the most common adverse effect of lithium therapy and occurs in up to 40% of patients.<sup>9</sup> Experimental studies in rodents have contributed to our understanding of the pathophysiology and time course of lithium-induced NDI.

### Water diuresis

In the rat kidney medulla, administration of lithium for 25 days induced a severe water diuresis with a marked (70%) downregulation of aquaporin 2 (AQP2) water channel expression, which was only partly reversed by stopping therapy, by thirsting or by administration of synthetic vasopressin (dDAVP).<sup>10</sup> This partial reversal is consistent with the clinical observations of slow recovery from lithium-induced urinary concentrating defects. Subsequent studies showed that the severity of lithium toxicity was time-dependent. During the first 2 weeks of lithium exposure, downregulation and lack of trafficking of AQP2 to the apical membrane were observed in the collecting duct without significant morphological changes; after 2 weeks, a major change in cell distribution along the collecting duct was observed, whereby the proportion of intercalated cells increased at the expense of principal cells.<sup>11–13</sup> In a subsequent study,<sup>14</sup> the lithium-induced increase in the density of intercalated cells was associated with an increase in the proliferation rate of principal cells rather than with a selective increase in the proliferation of intercalated cells, as was expected.

### Natriuresis

The pathophysiology of lithium-induced natriuresis is not well understood and might involve many factors. In the rat, treatment with lithium for 28 days resulted in polyuria, increased fractional excretion of sodium, and increased plasma aldosterone concentration; these changes were associated with a marked and highly segment-specific downregulation of the  $\beta$  and  $\gamma$  ENaC subunits in the cortical and outer medullary collecting duct.<sup>15</sup> In another study, lithium-induced NDI in rats was associated with a loss of  $\alpha$  ENaC subunit regulation by aldosterone, which might explain the association of chronic lithium treatment with sodium wasting.<sup>16</sup>

### Metabolic acidosis

Prolonged lithium treatment of humans and rodents sometimes results in hyperchloremic metabolic acidosis, which is believed to be caused by diminished net proton secretion in the collecting duct or excessive back-diffusion of acid equivalents, or both. Consistent with this theory, the expression of several renal acid–base

### Key points

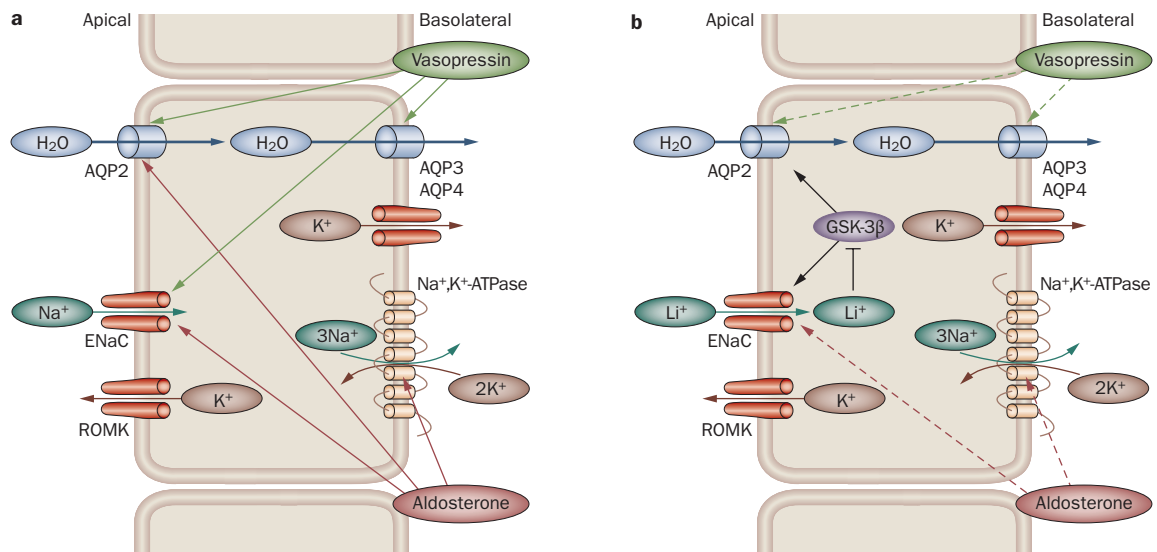
- Nephrogenic diabetes insipidus (NDI) is a very common adverse effect of lithium therapy in psychiatric patients
- Chronic kidney disease is a frequent and serious adverse effect of long-term lithium exposure
- The principal cells of the collecting duct are the primary target for the cytotoxic effects of lithium, which are thought to involve inhibition of signaling pathways that involve glycogen synthase kinase type 3 $\beta$
- The epithelial sodium channel (ENaC) is the primary site of entry for lithium into the collecting duct; therefore, blockade of the ENaC by amiloride might prevent the nephrotoxic effects of lithium
- Amiloride should be considered the treatment of choice for lithium-induced NDI and should be investigated for the prevention of lithium-induced nephropathy

transporters was altered in rats with lithium-induced NDI.<sup>12</sup> These changes are likely to represent direct or compensatory effects that aim to increase the capacity for bicarbonate reabsorption, ammonium reabsorption, and proton secretion to prevent the development of systemic metabolic acidosis.

### Pathophysiology

Collectively, the above data indicate that lithium causes dysregulation of AQP2 expression and trafficking along the entire collecting duct, which is accompanied by dysregulation of ENaC expression in the cortical collecting duct (Figure 1) and outer medullary collecting duct but not in the distal convoluted tubule, connecting tubule or inner medullary collecting duct.

The molecular mechanisms underlying lithium-induced water and sodium diuresis are far from well established. The reduced expression of AQP2 might be related to a decrease in interstitial osmolality<sup>17</sup> but such a decrease is unlikely to explain the trafficking defect. Lithium inhibits glycogen synthase kinase type 3 $\beta$  (GSK-3 $\beta$ ) activity and promotes cyclo-oxygenase 2 (COX-2)-dependent polyuria;<sup>18</sup> however, expression of cyclo-oxygenase 1 (COX-1), COX-2, and microsomal prostaglandin E synthase is markedly reduced in the inner medullary collecting duct of rats with lithium-induced NDI.<sup>19</sup> A reasonable working hypothesis would be that lithium interferes with the cAMP–protein kinase A (PKA)-dependent recruitment of AQP2 to the apical membrane of collecting duct cells. However, a 2006 study showed that the development of lithium-induced NDI was dissociated from adenylyl cyclase activity.<sup>20</sup> This observation could be explained by a specific compartmentalization effect mediated by PKA-anchoring proteins, which allows the cAMP–PKA pathway to have different effects at different times and at different cellular locations.<sup>21</sup> Total cellular cAMP content would not, therefore, be relevant to the observed pathophysiology. Alternatively, lithium could target receptors and proteins downstream of cAMP generation. A recent proteomic analysis of the inner medullary collecting ducts of rats treated with lithium for 1 or 2 weeks demonstrated that components of



**Figure 1** | Transport of sodium, potassium and water in a principal cell of the cortical collecting duct under physiological conditions and in the presence of lithium. Under physiological conditions **a** | sodium crosses the apical membrane through ENaC along an electrochemical gradient. Sodium is actively exported from the cell by the Na<sup>+</sup>,K<sup>+</sup>-ATPase. Entry of water is mediated by AQP2 and exit of water occurs through AQP3 and AQP4. Transport of both sodium and water is controlled by aldosterone and vasopressin. Potassium enters the cell through the Na<sup>+</sup>,K<sup>+</sup>-ATPase and is recycled by potassium channels. Potassium is secreted through a ROMK, along the electrochemical gradient created by the entry of sodium. During lithium treatment **b** | lithium crosses the apical membrane through ENaC, which prevents sodium entry. Lithium, unlike sodium, is not exported from the cell by the Na<sup>+</sup>,K<sup>+</sup>-ATPase; therefore, it accumulates intracellularly, leading to inhibition of GSK-3β. This enzyme controls water transport via AQP2 and sodium transport via ENaC. As a result of lithium's effects, the cell becomes at least partially insensitive to the actions of aldosterone and vasopressin. Abbreviations: AQP2, aquaporin 2; AQP3, aquaporin 3; AQP4, aquaporin 4; ENaC, epithelial sodium channel; GSK-3β, glycogen synthase kinase type 3β; Na<sup>+</sup>,K<sup>+</sup>-ATPase, sodium–potassium-transporting ATPase; ROMK, renal outer medullary potassium channel.

several signaling pathways, including protein kinase B (Akt) and mitogen-activated protein kinases, are activated by lithium treatment.<sup>20</sup> Interestingly, lithium treatment increased the intracellular accumulation of β-catenin as well as increasing levels of phosphorylated (inactive) GSK-3β.<sup>22</sup>

**Role of GSK-3β**

GSK-3β is involved not only in glycogen metabolism, but also in a large number of other cell functions.<sup>23</sup> Lithium sensitivity is a classic property of the enzyme; *in vitro*, its activity is inhibited by 50% in the presence of a lithium concentration of 1–2 mmol/l. The evidence in support of the critical role of GSK-3β as a molecular target for lithium-mimetic drugs has been reviewed elsewhere.<sup>24</sup> GSK-3β haploinsufficiency mimics the behavioral and molecular effects of lithium,<sup>25</sup> which supports a central role for GSK-3β in mediation of the therapeutic responses to lithium. Could the renal toxicity of lithium also be explained by inhibition of GSK-3β activity? To answer this question, we will need to determine whether the intracellular concentration of lithium in the collecting duct can reach a high enough level to inhibit GSK-3β substantially. Our present working hypothesis predicts that intracellular lithium concentration in the collecting duct is markedly increased by lithium treatment.

**Role of ENaC**

The apical entry of sodium into cells of the collecting duct is mediated by ENaC, which is permeable only to sodium and lithium. This channel's permeability to lithium is 1.5–2-fold higher than its permeability to sodium. Sodium is exported from the interior of the cells into the blood by the sodium–potassium-transporting ATPase (Na<sup>+</sup>,K<sup>+</sup>-ATPase) located on the basolateral membrane, but lithium is a poor substrate for this pump. Toxic intracellular levels of lithium could, therefore, build up quickly in cells of the collecting duct that are exposed to therapeutic concentrations of lithium (0.6–1.2 mmol/l). Preliminary experiments both *in vitro* and *in vivo* support this conclusion.

Transgenic mice whose collecting ducts lacked αENaC expression and littermate controls with normal ENaC function were fed lithium 40 mmol/kg of dry food for 25 days.<sup>26</sup> During lithium treatment, water intake in the transgenic mice increased only slightly, whereas the control mice showed a marked (fourfold) increase in water intake. At day 24, control mice exhibited marked polyuria, which was not seen in the transgenic mice. This protection from lithium-induced polyuria by genetic ablation of functional ENaC in the collecting duct supports the idea that ENaC-mediated lithium entry into the principal cells is a crucial step in the pathogenesis of lithium-induced NDI. Why other nephron segments that

express ENaC on their apical membrane (that is, the final part of the distal convoluted tubule and the connecting duct) are not sensitive to the toxic effects of lithium is, however, unclear. A nephron-segment-specific difference in the efflux of lithium from the cells or in the sensitivity of GSK-3 $\beta$  to lithium (or both) must exist.

### Treatment

Blockade of ENaCs by amiloride should inhibit the entry of not only sodium but also lithium into the principal cell. The effect of amiloride on renal medullary osmolytes, aquaporins, and urea transporters in rats fed lithium over 4 weeks to induce NDI has been investigated.<sup>27</sup> Concurrent administration of amiloride in drinking water restored urine osmolality and reduced urine volume.<sup>27</sup> A placebo-controlled, crossover trial in patients with bipolar disorder who received lithium showed that amiloride (10 mg daily for 6 weeks) significantly increased maximal urinary osmolality in a dDAVP-stimulated urinary concentrating test.<sup>28</sup> This study confirmed the observation made in 1985 that amiloride might represent a specific therapy for polyuria in lithium-treated patients, and might obviate the need for potassium supplementation in this setting.<sup>29</sup> Collectively, these data indicate that amiloride should be considered the preventive and therapeutic agent of choice for lithium-induced NDI.

### Lithium-induced nephropathy

Although the link between lithium and chronic renal failure was long disputed in the past, the long-term risk of CKD in lithium-treated patients has now been unequivocally established by epidemiological, clinical and histopathological studies.<sup>8</sup> Lithium-induced CKD occurs mostly in patients who have been receiving lithium for more than 10–20 years; occasionally, renal insufficiency develops earlier (within 10 years of lithium initiation).<sup>8</sup> The peak age of onset of bipolar disorder is 15–24 years, although many patients have a 5–10 year interval before treatment is initiated.<sup>1,2</sup> In a 2007 study, 14% of patients (total  $n = 480$ ) developed bipolar disorder in childhood (age 12 years or under), and 36% experienced onset in adolescence (age 13–18 years).<sup>30</sup> Thus, a large number of patients have been receiving lithium salts for 20–30 years or more by the time they reach middle age, and are at risk of developing CKD.

Two multicenter studies were performed by the same group in Sweden, 12 years apart, to investigate the prevalence of lithium-induced nephropathy.<sup>31,32</sup> After a mean treatment duration of 6.5 years, only 4% of patients had elevated serum creatinine levels, whereas this proportion increased to 12% after 19 years of exposure.<sup>1,2</sup> In a 2004 study, 21% of patients treated with lithium for a mean of 16.8 years (total  $n = 114$ ) had a serum creatinine concentration of 133  $\mu\text{mol/l}$  or more on two consecutive occasions.<sup>33</sup> Such a threshold clearly underestimates the prevalence of renal functional impairment. The above-mentioned studies were all conducted in

psychiatric clinics; by contrast, in a laboratory database study, a very high percentage of lithium-treated outpatients had a low estimated GFR ( $<60 \text{ ml/min/1.73 m}^2$ ), ranging from 39% in the 20–39 year age-group to 85% in patients aged over 70 years.<sup>34</sup> Susceptibility to the nephrotoxic effects of lithium differs from one patient to another for unidentified reasons.

### Pathology

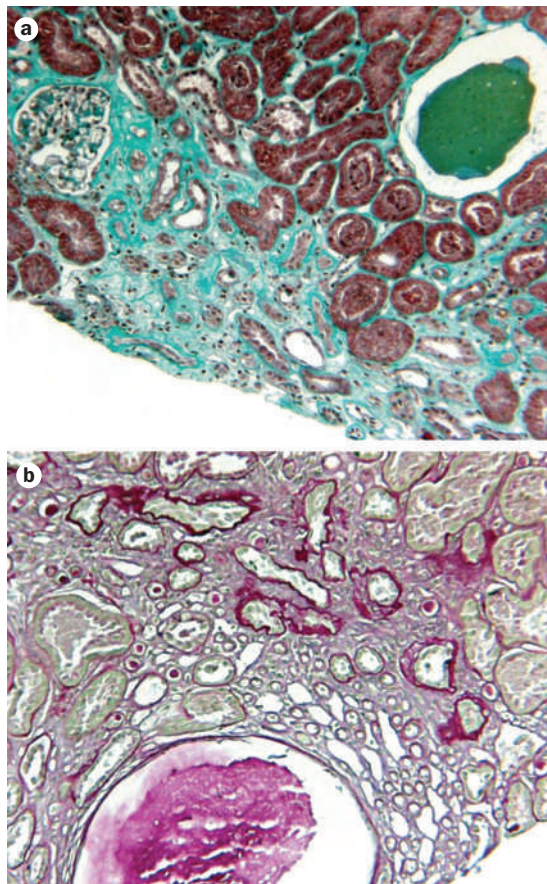
Lithium-induced nephropathy is of the chronic tubulointerstitial type (Figure 2). This pathology was first demonstrated in 1977 on renal biopsy specimens from 14 patients who had been treated with lithium for approximately 2–15 years.<sup>35</sup> Renal damage was subsequently documented in other studies,<sup>8,36</sup> which confirmed that interstitial fibrosis can appear as early as 5 years after initiation of this therapy.<sup>8</sup> Lesions of focal segmental glomerulosclerosis (FSGS) were often associated with the tubulointerstitial changes.<sup>36</sup> Renal cysts, which originate mainly from the distal tubule and collecting duct, are often found on renal biopsy specimens (Figure 2b) and MRI scans from lithium-treated patients.<sup>37</sup> Interestingly, GSK-3 $\beta$ , in concert with von Hippel–Lindau tumor suppressor protein, is a central regulator of the microtubule dynamics that are involved in the maintenance of primary cilia.<sup>38</sup> As discussed above, lithium inhibits GSK-3 $\beta$ . Primary cilia disturbances might trigger cyst formation, as has been suggested to occur in inherited cystic kidney diseases.

### Presentation and risk factors

Lithium-induced nephropathy is typically asymptomatic. Blood pressure is normal, urinary sediment is near normal and proteinuria is absent or minimal, except in patients with FSGS.<sup>36</sup> Such individuals should be differentiated from those with the very rare condition, lithium-induced minimal-change acute nephrotic syndrome, which has been reported in only 26 patients.<sup>36</sup> Urinary concentrating ability is impaired in patients with lithium-induced nephropathy, although severe NDI is not consistently found.

The only well-established predisposing factor to lithium-induced nephropathy is long-term lithium administration.<sup>8</sup> Other possible risk factors include age, episodes of lithium intoxication and comorbid disorders.<sup>3</sup> The daily dose of lithium is not a strong predictor of nephrotoxic effects. Once-daily regimens seem to be better tolerated than more-frequent (for example, twice-daily) dose regimens, but this finding has not been unanimously reported or prospectively tested. The diagnosis of lithium-induced nephropathy should be made if tubulointerstitial nephritis is found in a patient who has been receiving lithium for 10–20 years or more, and other causes of renal disease have been excluded. The finding of multiple, small renal cysts on imaging is suggestive but not specific for lithium-induced nephropathy.<sup>37</sup>

The progression of lithium-induced nephropathy is slow (the estimated decline in creatinine clearance



**Figure 2** | Renal biopsy specimens from a patient with lithium-induced nephropathy. **a** | Interstitial fibrosis and thickened tubular basement membranes surround an area of mild pathological changes that contains a small cyst (Masson trichrome stain; magnification  $\times 100$ ). **b** | A large cyst is located in a region where basement membranes have thickened as a result of tubular atrophy (periodic acid-Schiff stain; magnification  $\times 100$ ). Permission obtained from Dr Laure-Hélène Noël, Hôpital Necker.

is 2.2 ml/min per year),<sup>8</sup> although the condition can progress to end-stage renal disease (ESRD) over several decades. In series of highly selected patients followed up at nephrology clinics, 15–30% progressed to ESRD within an average of 20 years.<sup>8</sup> According to limited data from dialysis registries in Australia and New Zealand, the incidence of lithium-induced ESRD ranged from 0.2% to 0.7% in 2000–2003.<sup>8</sup> The mean age at onset of ESRD was 65 years, and dialysis was initiated on average 20 years after the start of lithium therapy.<sup>8</sup>

### Pathophysiology

The mechanisms of the chronic nephrotoxic effects of lithium, like those of its therapeutic activity, are poorly understood, but both effects might partly involve the same pathways. As well as inhibiting GSK-3 $\beta$ , lithium inhibits the activity of inositol monophosphatase, which results in depletion of inositol and inhibition of cell-cycle progression.<sup>39</sup> Accumulation of lithium in cells of the

distal nephron and early collecting duct via ENaC could account for the chronic nephrotoxic effects.

### Treatment

Lithium-induced nephropathy can be detected if psychiatrists request serum creatinine measurements and refer patients with elevated creatinine levels and decreased GFR to nephrologists. However, renal monitoring of patients receiving prolonged lithium treatment is still insufficient in most countries. In a 2008 survey in Paris, only 59% of lithium-treated patients had one or more serum creatinine measurements taken over an 8 year period.<sup>34</sup> The efficacy of lithium therapy in bipolar disorder is so good that some patients are lost to follow-up, regular biochemical monitoring is not performed, and renal failure is discovered too late. The practice guidelines of the American Psychiatric Association recommend measurement of serum creatinine level every 2–3 months during the first 6 months of lithium therapy and every year thereafter.<sup>3,40</sup>

Detection of impaired renal function in a patient receiving lithium raises a dilemma. The decision to substitute lithium with another mood stabilizer should be made jointly by the patient, the psychiatrist and the nephrologist. All guidelines conclude that lithium is still the first-line therapy, the ‘quintessential mood stabilizer’, for the prophylaxis of recurrence of bipolar affective disorder.<sup>1</sup> Some patients, whose illness has been well controlled for decades by lithium, refuse to consider interruption or substitution of this therapy. Furthermore, the risk of suicide or early recurrence of bipolar illness following discontinuation of lithium seems to be high.<sup>8</sup> The efficacy and tolerability of other mood stabilizers (valproate, lamotrigine, olanzapine and, to a lesser extent, carbamazepine)<sup>41,42</sup> are different from those of lithium and can only be partly predicted. In addition, the beneficial renal effect of interrupting lithium administration might be observed only in patients with moderate CKD (that is, serum creatinine level  $< 220 \mu\text{mol/l}$ <sup>36</sup> or estimated creatinine clearance  $> 40 \text{ ml/min}$ <sup>8</sup>). In other cases, renal failure progresses after lithium discontinuation at the same rate as during lithium administration. A point of no return probably exists, after which renal fibrosis continues to progress despite removal of the triggering insult. The potential detrimental psychiatric consequences of withdrawing lithium should, therefore, be balanced against its potential beneficial renal effect on a case by case basis. Other predictors of poor renal prognosis, besides renal function, are the extent of interstitial fibrosis on renal biopsy and the presence of heavy proteinuria (which should be managed with antiproteinuric drugs). If lithium is continued, serum levels of this element should be carefully monitored, and regular renal follow-up should be organized, as for any patient with CKD.

Whether amiloride can prevent the medium-term adverse effects of lithium (metabolic acidosis and cytotoxic effects on principal cells) and the long-term effect of lithium-induced nephropathy remains to be

determined. If such a preventive action is identified, this finding would strongly argue that lithium exerts a primary cytotoxic effect that is limited to the principal cells of the collecting duct and mediated by the entry of lithium through ENaCs.

## Lithium-induced hypercalcemia

### Presentation and risk factors

First described in 1973,<sup>43</sup> lithium-induced hypercalcemia was not attributed to hyperparathyroidism (that is, high serum parathyroid hormone [PTH] level or inadequate serum PTH level in relation to the serum calcium level) until 1978.<sup>44</sup> Up to 25–30% of lithium-treated patients develop mildly increased serum calcium-ion concentrations. ‘False’ hypercalcemia due to plasma volume depletion resulting from NDI should be excluded in such individuals. The prevalence of lithium-induced hypercalcemia is highest in patients with renal failure, in whom calciuria is reduced; unselected patients have a comparatively low prevalence (7–10%) of this condition.<sup>8</sup> Nephrolithiasis or nephrocalcinosis can complicate hypercalcemia.

The prevalence of hyperparathyroidism was 7.5 times higher in lithium-treated Swedish patients than was expected in the Swedish general population; the prevalence was also 7.5 times higher when data from only the women in each population aged 60 years or more (who have the highest prevalence of hyperparathyroidism) were analyzed.<sup>45</sup> The prevalence of hyperparathyroidism in chronic lithium users (>10 years) has been estimated at approximately 10–15% in retrospective case series.<sup>46</sup>

### Treatment and pathophysiology

Discontinuation of lithium does not decrease serum calcium level in the short term,<sup>7,45</sup> which is not surprising because hyperparathyroidism is due to anatomical lesions: single adenomas in two-thirds of cases, and multiglandular hyperplasia in the remaining third.<sup>46</sup> In a 2005 series, multiglandular disease was documented in 50% of lithium-treated patients with hyperparathyroidism—a much higher percentage than in patients from the general population with hyperparathyroidism.<sup>46</sup> Ablation of a single parathyroid adenoma usually leads to normocalcemia, even in patients who continue to receive lithium.<sup>46</sup> Long-term studies are, however, not available to evaluate the risk of recurrence of hypercalcemia. Surgical treatment of multiglandular disease is technically difficult and hazardous.

The mechanism of lithium-induced hyperparathyroidism is not well understood. Lithium might directly stimulate PTH production. Alternatively, lithium presumably interferes with calcium-mediated transmembrane signal transduction by the calcium-sensing receptor, because it induces a reduction in the set point for PTH secretion. The similarity between lithium-induced hypercalcemia and familial hypocalciuric hypercalcemia (which is associated with inactivating mutations in the gene encoding the calcium-sensing receptor) has been underlined.<sup>47</sup>

However, lithium-induced hypercalcemia might also be caused by hypocalciuria as a result of mild renal function impairment. The calcimimetic drug, cinacalcet hydrochloride, an allosteric activator of the calcium-sensing receptor, decreases or normalizes serum calcium but only modestly reduces serum PTH levels in lithium-treated patients with hypercalcemia<sup>47,48</sup> similar to its effect in those with primary hyperparathyroidism.<sup>49</sup> The exact interaction between lithium, the calcium-sensing receptor and cinacalcet is unknown, and large studies are necessary to clarify the mechanisms involved and to assess the clinical relevance of cinacalcet in this setting. Most lithium-treated patients with mild hypercalcemia do not consent to interruption of their lithium therapy, and continuation of lithium does not abolish the action of cinacalcet on serum calcium level.<sup>48,49</sup> Cinacalcet might be of particular use in patients with multiglandular disease. A decrease in serum calcium concentration prevents rare cardiac rhythm disorders that can be triggered by both hypercalcemia and lithium.<sup>40,50,51</sup>

Serum levels of thyroid-stimulating hormone should be monitored every 6–12 months in all patients receiving lithium, to detect hypothyroidism. Serum calcium levels should be measured every 1–2 years to detect hypercalcemia.

## Conclusions

Lithium is widely used in the treatment of bipolar spectrum disorders and refractory unipolar major depression. The adverse renal effects of lithium include NDI, metabolic acidosis, chronic nephropathy and hypercalcemia. NDI and metabolic acidosis tend to occur within weeks or months of lithium initiation, whereas chronic nephropathy and hypercalcemia are most likely to develop after years of lithium exposure. Clinical, genetic and experimental evidence indicate that ENaCs expressed along the collecting duct have a central role in the pathophysiology of lithium-induced NDI by facilitating the intracellular accumulation of lithium, which perhaps leads to inhibition of GSK-3 $\beta$ . This finding provides the rationale for treatment of lithium-induced NDI with amiloride. Long-term studies should be conducted to establish whether amiloride can also prevent the appearance of lithium-induced nephropathy and CKD, and whether cinacalcet could be useful in the treatment of lithium-induced hypercalcemia. The decision to discontinue lithium in a patient with declining kidney function should be carefully considered, particularly as renal function does not always improve after lithium withdrawal. Close collaboration between psychiatrists and nephrologists is essential to ensure the early detection and management of lithium-induced nephropathy.

### Review criteria

PubMed was searched for articles published up to 31 December 2008, using the keywords “lithium”, “toxicity”, “nephrogenic diabetes insipidus”, “ENaC”, “AQP”, “vasopressin”, “amiloride” and “GSK3”.

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