

# Successful Treatment of Lithium-Induced Nephrogenic Diabetes Insipidus with Celecoxib: A Promising Therapeutic Option

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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**Patient:** Female, 46-year-old  
**Final Diagnosis:** Diabetes insipidus • lithium intoxication  
**Symptoms:** Altered mental state  
**Clinical Procedure:** —  
**Specialty:** Nephrology

**Objective:** Unusual or unexpected effect of treatment  
**Background:** Nephrogenic diabetic insipidus (NDI) poses a challenge in clinical management, particularly when associated with lithium ingestion. Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used for the treatment of numerous diseases worldwide, including NDI. However, many studies have reported the diverse adverse effects of long-term use of non-selective NSAIDs. Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is a better drug to relieve pain and inflammation in terms of long-term safety and efficacy than non-selective NSAIDs. Nevertheless, there are few reports describing the effectiveness of celecoxib in treating NDI.

**Case Report:** We report a case of a 46-year-old woman with schizophrenia who presented with severe hyponatremia and refractory polyuria due to lithium-induced NDI. Cessation of lithium ingestion and traditional treatments, including trichlormethiazide and desmopressin, yielded minimal improvement in her hyponatremia and polyuria. Her sodium level needed to be strictly controlled with the infusion of dextrose 5% in water. Given the safety of celecoxib, we decided to initiate celecoxib as the treatment of lithium-induced NDI instead of indomethacin. Notably, the introduction of celecoxib led to a substantial and sustained amelioration of polyuria and hyponatremia without any celecoxib-associated adverse effects. Even after transfer to another hospital, stability in serum sodium levels persisted with celecoxib.

**Conclusions:** We presented a case of lithium-induced NDI successfully treated with celecoxib, a selective COX-2 inhibitor. To the best of our knowledge, this is the first reported case of successful treatment of lithium-induced NDI with celecoxib, and suggests celecoxib is a viable therapeutic option warranting further exploration. Physicians should consider its use when faced with the challenging management of lithium-induced NDI.

**Keywords:** Celecoxib • Diabetes Insipidus, Nephrogenic • Lithium

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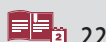
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## Introduction

Nephrogenic diabetic insipidus (NDI) is an endocrine disease in which a decrease in the urine- concentrating ability is caused by resistance to arginine vasopressin (AVP) [1,2]. The most common cause of acquired NDI is chronic ingestion of lithium, which remains a mainstay of treatment for bipolar disorder [3,4]. Epidemiological studies reveal that NDI occurs in up to 40% of patients taking lithium [5]. Thiazide diuretics, amiloride, and indomethacin have been used to treat lithium-induced NDI. Nonetheless, some cases appeared to be irreversible despite cessation of lithium intake [6].

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used for the treatment of numerous diseases worldwide. Among these medications, indomethacin, one of the cyclooxygenase (COX) non-selective NSAIDs, may have a better effect on NDI than other ones [5,7-9]. However, various complications may ensue with long-term use of COX non-selective NSAIDs. Many studies have reported its diverse adverse effects, such as gastroduodenal toxicity and bronchospasm [10,11]. COX-2 is an enzyme of prostaglandin-endoperoxide synthase identified in the early 1990s. Recent research has revealed the superiority of COX-2 selective NSAIDs over non-selective ones in terms of safety and efficacy [12-14]. These advantages have raised an exciting possibility to improve patient prognosis and quality of life in clinical practice.

Herein, we present a case of refractory lithium-induced NDI, successfully treated with celecoxib, a COX-2 selective NSAID.

## Case Report

A 46-year-old woman with schizophrenia was transferred from a mental health hospital because of severe hyponatremia. She

had been hospitalized in the previous hospital for treatment of psychotic exacerbation 5 days before the transfer. Her past medications included long-term lithium and levomepromazine, although the exact duration of lithium intake was unclear from her records. Her past medical history was insignificant other than schizophrenia. She never smoked or drank alcohol and had no history of substance abuse.

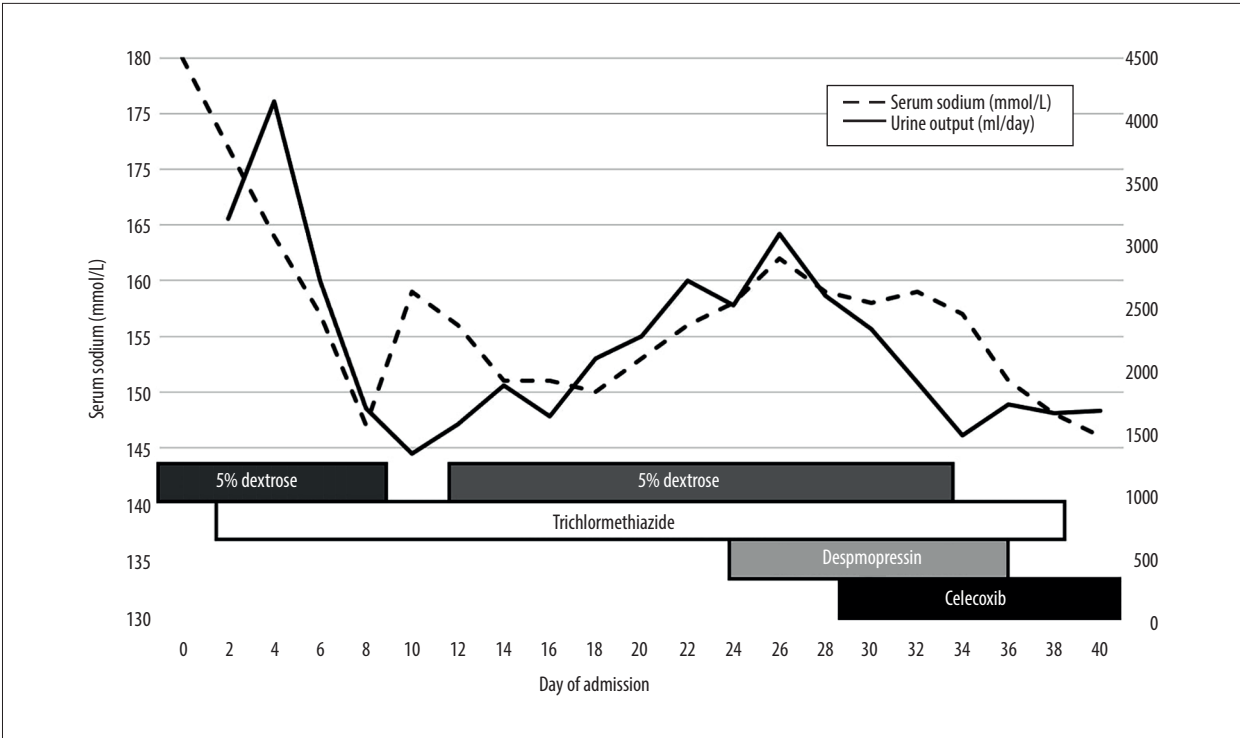
Upon examination, her temperature was 38.0°C, her pulse was 112/min and regular, her blood pressure was 130/89 mmHg, and her pulse oximetry on an O2 2L nasal cannula showed an oxygen saturation of 99%. She could not communicate due to confusion and agitation. Her blood laboratory test results showed a significantly elevated serum sodium level of >180 mmol/L, serum osmolality of 369 mOsm/kg H<sub>2</sub>O, urine sodium level of 65 mmol/L, and urine osmolality of 250 mOsm/kg H<sub>2</sub>O (**Table 1**).

Furthermore, she had polyuria of 3-4 liters per day, leading to prerenal kidney failure. She did not exhibit other electrolyte abnormalities. Her head and trunk computed tomography (CT) images revealed neither prominent intracranial nor internal organ diseases. These medical history and laboratory results raised the suspicion of lithium-induced nephrogenic diabetes insipidus. Thus, we discontinued her lithium treatment and administered trichlormethiazide and an infusion of dextrose 5% in water (D5W) to normalize her electrolyte balance. We controlled the amount of D5% infusion at around 1500 ml/day, depending on her sodium level and urine volume. A fluid deprivation test was not conducted due to concerns about worsening her condition.

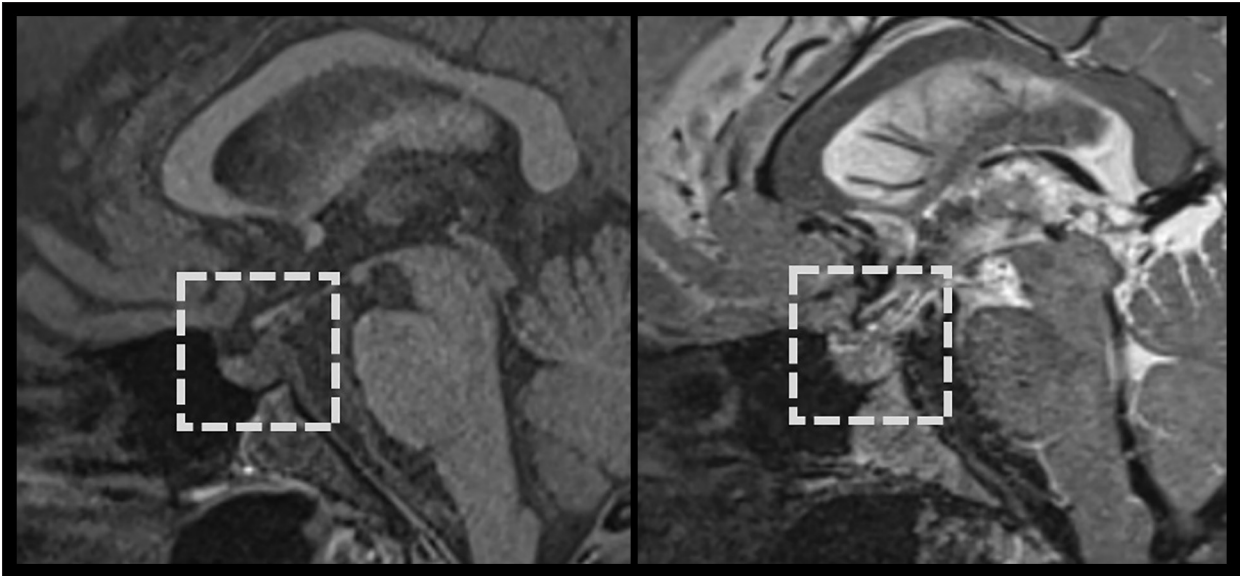
On the eighth day of follow-up, her sodium level improved, reaching 147 mEq/L with the D5W infusion rate controlled (**Figure 1**), but her serum level rose rapidly after discontinuing the D5W infusion. It was quite challenging to stabilize serum

**Table 1.** Blood and urine test results on admission.

Blood metabolic panel			Aspartate aminotransferase	(U/L)	60
Glucose	(mg/dL)	138	Alanine aminotransferase	(U/L)	71
Blood urea nitrogen	(mg/dL)	35	Total bilirubin	(mg/dL)	0.6
Creatinine	(mg/dL)	2.3	Serum osmolality	(mOsm/kg/H <sub>2</sub> O)	369
Sodium	(mmol/L)	>180	Urinary electrolytes		
Potassium	(mmol/L)	3.6	Urine sodium	(mmol/L)	65
Chloride	(mmol/L)	>120	Urine potassium	(mmol/L)	14
Calcium	(mg/dL)	10.3	Urine blood urea nitrogen	(mg/dL)	259
Protein	(g/dL)	7.9	Urine creatinine	(mg/dL)	32
Albumin	(g/dL)	3.8	Urine osmolality	(mOsm/kg/H <sub>2</sub> O)	250
Alkaline phosphatase	(U/L)	68			



**Figure 1.** Trend of serum sodium and urine output throughout hospitalization.



**Figure 2.** Head sagittal magnetic resonance imaging (MRI): **right** (T1-weighted MRI) **left** (T2-weighted MRI). Loss of posterior lobe signal on T1-weighted MRI (dashed square) indicates the possible central diabetes insipidus.

sodium levels without the D5W infusion. Additionally, serum AVP concentration on the first day of admission showed 2.8 pg/mL (normal range, 0.5-5.0 pg/mL), indicating there was no positive feedback AVP secretion. Her brain magnetic resonance imaging (MRI) scan also revealed low intensity in the posterior lobe of the pituitary on T1-weighted MRI, which was consistent with central diabetes insipidus (**Figure 2**). To determine

the cause of polyuria, we tried administering desmopressin nasal spray. Nevertheless, she remained polyuric, and her urine osmolality was not elevated. Her sodium level also did not improve despite the AVP administration. These results confirmed that the cause of her polyuria and electrolyte disorder was lithium-induced NDI.

**Table 2.** Blood and urine test results on day 40.

Blood metabolic panel			Aspartate aminotransferase (U/L)	21
Glucose	(mg/dL)	129	Alanine aminotransferase (U/L)	29
Blood urea nitrogen	(mg/dL)	19	Total bilirubin (mg/dL)	0.5
Creatinine	(mg/dL)	0.94	Urinary electrolytes	
Sodium	(mmol/L)	148	Urine sodium (mmol/L)	27
Potassium	(mmol/L)	4	Urine potassium (mmol/L)	32
Chloride	(mmol/L)	107	Urine blood urea nitrogen (mg/dL)	212
Calcium	(mg/dL)	9.2	Urine creatinine (mg/dL)	26
Protein	(g/dL)	6.6	Urine osmolality (mOsm/kg/H <sub>2</sub> O)	189
Albumin	(g/dL)	3.5		
Alkaline phosphatase	(U/L)	66		

**Table 3.** Published case reports of nephrogenic diabetic insipidus successfully treated with celecoxib.

Author	Publication year	Age/sex	Diagnosis	Medicines
Our clinical case	2023	46 years/F	Lithium-induced NDI	Trichlormethiazide, desmopressin, celecoxib
Tao et al [15]	2021	Newborn/M	Congenital NDI	Hydrochlorothiazide, celecoxib
Soylu et al [16]	2005	17 months/M	Congenital NDI	Hydrochlorothiazide, amiloride, celecoxib

Trichlormethiazide and desmopressin did not improve her sodium level, so we initiated celecoxib as the treatment of NDI on day 30. Subsequently, her diuresis decreased to 1500-2500 ml/day, and intravenous D5% could be stopped. Her hypernatremia also gradually and markedly resolved. Her Cre and eGFR showed no sign of deterioration and remained stable (Table 2). Although the urine test showed low osmolality, the stable sodium level and the decreased urine output indicated good control and improvement of NDI.

On day 44, she was transferred to another hospital for long-term psychiatric treatment. A few months after the transfer, we have not received any reports of celecoxib-associated adverse effects.

## Discussion

This female patient with schizophrenia suffered from refractory polyuria and hypernatremia after lithium ingestion. We administered trichlormethiazide and desmopressin to normalize her polyuria and electrolyte disorder due to lithium-induced NDI. However, these medications had only a minimal effect on her condition. Thus, she started receiving celecoxib on day 30, which dramatically and continuously improved her polyuria and hypernatremia. Even after her transfer to another

hospital, her serum sodium level remained stable with celecoxib. To the best of our knowledge, this is the first reported case of lithium-induced NDI successfully treated with celecoxib.

Although indomethacin has a significant effect on decreasing urine output in NDI patients, its long-term administration clearly causes undesirable effects, such as gastrointestinal bleeding and kidney failure. Celecoxib, a selective COX-2 inhibitor, can relieve pain and inflammation with fewer adverse effects than classical non-selective NSAIDs. Its efficacy and safety have been demonstrated in several high-quality randomized controlled trials with adequate sample sizes [10,11,13,14]. Thus, our case report's highlight is that celecoxib can also be safe and effective for the polyuria of lithium-induced NDI as well as inflammatory diseases.

However, only 2 case reports have indicated the effectiveness of celecoxib in treating congenital NDI (Table 3). Tao et al reported celecoxib worked effectively for congenital NDI in combination with hydrochlorothiazide [15]. Soylu et al also have shown celecoxib was successful for treating congenital NDI [16]. These case reports strongly support our opinion that celecoxib is effective and safe for treating lithium-induced NDI.

Regarding the pathophysiology of NSAIDs for nephrogenic diabetes, COX-2 is predominantly produced in various kidney

sites, including glomerular endothelium and medullary interstitial cells. Prostaglandin (PG) facilitates vasodilation of afferent arterioles and glomerulus and also inhibits the action of AVP of medullary interstitial cells [17]. Under the conditions of renal hypoperfusion, such as hypotension or chronic renal disease, PG synthesis increases to dilate renal afferent arterioles and glomerular vessels for adequate renal blood flow [18,19]. The COX inhibition by NSAIDs leads to decreased PG synthesis, resulting in renal vasoconstrictions and renal function decline. However, in patients without renal hypoperfusion, PG has little effect on renal hemodynamics [20,21]. Celecoxib, a selective COX-2 inhibitor, predominantly affects the medulla, inhibiting PG synthesis, increasing AVP action, and enhancing water absorption, as shown in our patient.

The limitation of this case report is that the low signal of the posterior pituitary lobe on T1-weighted MRI might be inconsistent with the diagnosis of lithium-induced NDI. However, the bright signal in this region is absent physiologically in some healthy individuals [22]. Additionally, our patient's clinical course and endocrine hormone results strongly deny the possibility of central diabetes insipidus.

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## Conclusions

In this report, we presented a case of lithium-induced NDI successfully treated with celecoxib, a selective COX-2 inhibitor. Given the advantages of celecoxib, physicians should consider its use when faced with the challenging management of lithium-induced NDI.

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