

## A true dialytic urgency: lithium intoxication

### *Intoxicación por litio, una verdadera urgencia dialítica*

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#### Abstract

Lithium carbonate is a drug widely used in Colombia for the treatment of various psychiatric pathologies such as treatment in patients with bipolar affective disorder, however its narrow therapeutic index predisposes to the occurrence of acute poisoning, unlikely to happen but could be fatal.

It should be said that its diagnosis requires a high rate of suspicion because it presents various clinical manifestations such as neuropsychiatric symptoms and even mental disorders of an organic type that can be complicated by an acute kidney injury requiring emergency dialysis therapy.

We report the case of a patient who presented to the emergency department with alteration in the state of consciousness in whom lithium poisoning was found and who required hemodialysis in an early stage.

In conclusion, in a patient with risk factor and therapy with this drug is very important to guide appropriate treatment, and also discard differential diagnosis, in order to avoid fatal consequences.

**Keywords:** Dialysis, poisoning, lithium, chronic kidney disease, fatal outcome, urinary bladder diseases.

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#### Resumen

El carbonato de litio es un fármaco ampliamente usado en Colombia para el tratamiento de varias patologías psiquiátricas, como es el caso del trastorno afectivo bipolar; sin embargo, su índice terapéutico estrecho predispone a intoxicación aguda. Aunque esta reacción rara vez ocurre, puede ser fatal.

El diagnóstico de intoxicación aguda por carbonato de litio requiere una alta tasa de sospecha, pues se presenta con varias manifestaciones como síntomas neuropsiquiátricos e incluso desórdenes mentales, que pueden complicarse por injuria renal aguda requiriendo terapia dialítica emergente.

A continuación se presenta el caso de una paciente que se llegó al servicio de urgencias con alteración en el estado de conciencia. Finalmente, se diagnosticó intoxicación por litio y la mujer requirió hemodiálisis.

En conclusión, en un paciente con factores de riesgo y terapia con este medicamento es muy importante guiar un manejo apropiado y descartar diagnósticos diferenciales, esto con el fin de evitar consecuencias fatales.

**Palabras clave:** diálisis, intoxicación; litio, enfermedad renal crónica, resultado fatal, enfermedades de la vejiga urinaria.

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## Introduction

Lithium is a chemical element located in group one (alkali metal) of the periodic table. This specific location enables it to ionize into a cation and easily interact with other functional groups. In addition, it is the lightest metal (74 Daltons), making it easy to be distributed throughout the body<sup>1</sup>. Its use in the treatment of mental disorders began in 1948 by Doctor John Cade in Australia<sup>2</sup>. Since then, lithium salts were classified as mood stabilizers due to its positive empiric impact on the treatment of bipolar affective disorders with a success rate of 80% in the treatment of both maniac and depressive symptoms<sup>3,4</sup>.

## Case report

A 77 year old woman, with personal history of affective bipolar disorder in treatment with

lithium, presented into our hospital with functional decline, somnolence, fever and tremor, for 5 days approximately. The physical examination showed altered consciousness state, normal blood pressure, tachycardia, tachypnea, grade II dehydration, neck rigidity, tremor and hyperreflexia with clonus. The rest was normal.

Because the hospital was of first level, basic laboratories were available, so initially there was focus like meningitis, so antibiotics are started after blood and urine samples were collected. We observed leukocytosis with neutrophilia, altered renal function with GFR in 27.08 ml/min/1.73 m<sup>2</sup> with MDRD formula (**figure 1**), proteinuria, hematuria and massive bacteriuria in the urine sediment. Also glycemic levels and an electrocardiogram were realized, finding in the last one sinus tachycardia, normal ventricular axis, interval PR of 180 milliseconds, but a corrected interval QT of 510 milliseconds.

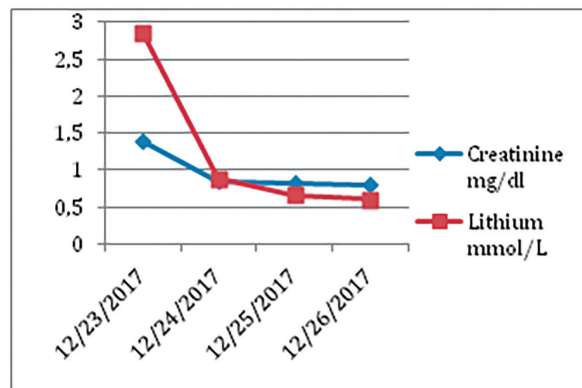


Figure 1. Laboratories

In this moment, with these findings, acute lithium intoxication was suspected associated with acute kidney injury and urinary tract infection, considered like an emergency dialysis. Immediately the patient was translated to a hospital with the service of nephrology and dialysis, and realized serum lithium levels finding an abnormal value of 2.85 mmol/L (Figure 1) (normal value 0.6 – 1.2 mmol/L). So,

it was decided to initiate dialysis femoral via and antibiotic, presenting good response. In urine culture was isolated *Proteus Mirabilis*, so regimen antibiotic with Aztreonam was gave during 10 days with resolution of the infection.

After three days of treatment, renal function and serum lithium level were normal.

## Discussion

Lithium distribution volume ranges between 0.6-0.9 L/Kg in the average adult. It has no protein or tissue binding, making it a substance with a therapeutic index that ranges between 0.6-1.5 mEq/L, which is very narrow<sup>3</sup>. Particularly, the optimal steady-state concentration of lithium for treatment of bipolar disorders is 0.6-1.2 mEq/L. Lithium acts with inositol and glycogen synthase kinase 3, by inhibiting an enzyme called inositol monophosphatase, decreasing inositol levels and altering first and second messenger system. With the chronic administration, stabilize GABA reuptake, explaining the effect on mania. Also antagonize 5HT1A and 5HT1B receptors, increasing levels of serotonin, explaining the effect on depression symptoms. Maintaining these exact ranges may be challenging and chances of toxicity remain high. Lithium is excreted in its vast majority by the kidneys and because of its chemical resemblance to sodium; they are handled in a very similar way. It is freely filtered and 60% of it is reabsorbed in the proximal tubule<sup>5</sup>. Due to its high rate of reabsorption and distribution throughout the body, lithium's half-life may be as high as 18 and 36 hours in the adult and the elderly, respectively<sup>5</sup>.

As explained in the pharmacokinetics section, lithium has several biological interactions that may lead to lithium toxicity. The average patient on chronic lithium treatment may experience at least one episode of toxicity during his lifetime<sup>6</sup>. Lithium toxicity is classified by most authors in three different types: Acute, which includes manifestations that are predominantly gastrointestinal, such as nausea, vomiting and diarrhea, but neuromuscular manifestations may also be present; Acute on chronic, in which both gastrointestinal and neurologic manifestations occur; and Chronic that includes manifestations primarily neurological, including sluggishness, ataxia and neuromuscular excitability<sup>7</sup>.

Toxicity is explained mostly by abnormally reduced excretion in the kidneys, overdose, prescribing errors and drug-to-drug interactions. Lithium has no protein or tissue binding, therefore, hemodialysis provides a useful therapeutic strategy<sup>8</sup>.

At the intracellular level, lithium ion is transported from the lumen to the intracellular space by different protein channels, by means of an exchanging cation pump, in substitution of either sodium or potassium. The H<sup>+</sup>/Na<sup>+</sup> exchanger accounts for most of the lithium transported into the cytosol and posteriorly to the blood. Particularly, lithium entrance is handled by passive transports compared to its exit, which is handled by pumps involving active transport and energy use. Secondary to this pump imbalance, lithium tends to accumulate throughout the body: Other channels might also contribute to the accumulation of Lithium, such as Glucose/Na channel or Na/K ATPase<sup>9</sup>.

Back to our patient: Our patient developed an urinary tract infection (UTI), particularly a pyelonephritis, as manifested by its systemic symptoms, clinical findings and urinalysis findings. According to classification criteria, our patient met criteria urosepsis etiology. Its urine culture was found to be positive for *Proteus Mirabilis*, a facultative anaerobe bacteria, urease positive with increasing rates of antibiotics resistance<sup>10</sup>. Because of the pyelonephritis, induced renal impairment manifested as reduced GFR and an increased reabsorption (secondary to its sepsis induced vasodilation and dehydration), leading to increased lithium levels up to 2.85 mEq/L.

The main stem for treatment of acute lithium toxicity relies on following the ABC protocols (Airway, Breath, Circulation) and supportive care, followed by aggressive hydration in order to guarantee appropriate lithium clearance. Hydration should be done with normal saline (0.9%). Sodium levels should be assessed prior to treatment because these patients may develop induced nephrogenic diabetes insipidus, which makes it important to have a baseline serum sodium level upon hydration. Treatment with oral charcoal is not recommended by most authors<sup>11</sup>. Some studies have shown a benefit of giving high doses of kayexelate (oral sodium polystyrene sulfonate) is reducing lithium levels, however, its use is not recommended secondary to the side effects of hypokalemia<sup>12</sup>. Ultimately, the gold standard treatment when these therapies fail is the use of hemodialysis as an extracorporeal measure. Consensus guidelines for the use of hemodialysis in this setting are controversial. Some authors suggest using hemodialysis in patients with

lithium levels greater than 5 mEq/L and a normal renal function. In those with impaired renal function (creatinine higher than 2 mmol/L) and lithium levels of 4 mEq/L, therapy can be considered as well<sup>13</sup>. Finally, those patients who don't respond to previous treatment and in whom signs of toxicity persist, hemodialysis remains as a reasonable option. More studies are needed to provide guidelines with a stronger degree of recommendation<sup>14</sup>.

In our patient, the lithium levels quickly fell after hemodialysis, from 2.85 to 0.89 mEq/L in a 24-hour period. Additionally, the BUN and creatinine levels also fell down to normal after the prerenal acute kidney injury was solved. Creatinine and BUN decreased from 1.89 to 0.85mg/dl and from 43 to 17mg/dl respectively, in a 48-hour period.

## Conclusion

Patients treated for bipolar affective disorder with lithium must be specifically warned on how to early identify possible triggers that may induce acute kidney injury, such as UTI, systemic infections, volume depletion states patients must stop medication and seek medical care.

Detailed clinical history of patients initial neurological disorders before initiating Lithium therapy is required, since lithium intoxication symptoms tend to be mostly neurological, so there must be a clear differentiation between the treated pathology symptoms and the newly acquired intoxication symptoms for the diagnosis to be possible and timely. In this case, there were three potential triggers for the GFR drop: Pyelonephritis, prerenal acute kidney injury and prolonged lithium exposure. The summation of these caused Lithium serum levels to increase to toxic levels and resulted in an intoxication, however, the dehydration had the most evident repercussions.

## Contribution of each author

Carlos Aníbal Restrepo: In charge of drafting the discussion section compiling the ideas of all the authors. Was also in charge of investigation and evidence to support all the arguments presented.

Maria Antonia Rico: In charge of providing the background information part of the discussion. Also was crucial in the search for evidence and other articles that supported our thesis about the fisiopathology of the intoxication.

Juan Simon Rico: Was the main editor of the paper in charge of retouching and approving the final product. Also contributed with ideas and structure for the development of the whole paper, both discussion and introduction.

Mariana Montoya Castillo, Diana Carolina Echeverri Díaz and Felipe Osorio Ospina: Came up with the idea of presenting the case. Mariana was in charge of collecting all the information regarding our patient. They drafted the introduction of the paper which included all the clinical history of the patient in order to develop a sustained discussion and conclusions.

## Conflicts of interest

The authors have no conflicts of interest of any type, nor have any relation with the pharmaceutical industry that could bias the manuscript.

The authors didn't receive financing for the development of the paper and no one else is in any way involved with the article.

## Ethical responsibilities

### Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

### Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

The authors certify that we do not have conflicts of interest

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The authors confirm that each one contributed with all the material included in the article

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