







Lithium poisoning. State of the art.

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Abstract

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Introduction: Lithium has been used for more than a century for mood disorders; it is the treatment of choice for bipolar affective disorder. One of its drawbacks is its narrow therapeutic index and the complications associated with supratherapeutic concentrations, which is why lithium poisoning is frequent. Clinical suspicion, clinical manifestations, and measurement of lithium levels are essential for diagnosis. Treatment includes supportive measures and renal support therapies.

Objective of the review: The aim is to provide the reader with an update on diagnostic and therapeutic approaches to lithium-induced poisoning.

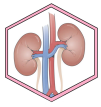
Methods: A systematic search was carried out in various sources: PubMed (Medline, United States Library of Congress), Science Direct, Scopus, Embase, and Lilacs; the search was restricted to references in Spanish and English, with no publication date limit. Keywords in English and Spanish were used. The different authors reviewed the references found in the search to proceed with elaborating on the document later.

Conclusion: Lithium poisoning is a frequent entity with high morbidity and mortality; in many cases, it can be prevented with adequate follow-up and periodic lithemia. Carrying out adequate treatment is the best tool to avoid irreversible complications, especially when starting renal support therapy is indicated since it continues to be the best therapeutic option in severe poisoning.

Keywords:

MESH: Lithium, Lithium Compounds, Toxicity, Renal Dialysis.

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Lithium is the first line of treatment for bipolar affective disorder [1-5]. The plasma lithium level is susceptible to minimal changes in renal function [6]. The adverse effects of lithium administration are lithium-induced nephrogenic diabetes insipidus and lithium nephropathy, which have significant associated morbidity [7]. This review aims to explore current issues in treating poisoning by this psychoactive drug.

Generalities and epidemiology

The use of lithium has been documented in more than 40 years of experience in treating mood disorders, although its prescription has been reduced over time [5]. This drug was approved by the Food and Drug Administration of the USA in 1970 and is still considered the drug of choice for treating bipolar affective disorder [2, 3]. One of its drawbacks is the narrow therapeutic index and the complications associated with its supratherapeutic concentrations [4].

According to the records of the American Association of Poison Control Centers, approximately 6,000 to 7,000 cases of lithium poisoning occur each year [8], of which the incidence of moderate to severe lithium poisoning is 7.16% with at least one episode of serum lithium concentrations ≥ 1.5 mmol/L. Of this group of patients, 34% required admission to high-dependency units, and 13% required renal replacement therapy through hemodialysis, representing an incidence of 0.01 patient-years [9].

Mechanism of action and pharmacokinetics

Mechanism of action

The mechanism of action of lithium has yet to be fully described. The clinical consequences reflect effects on transduction pathways related to glutamate, inositol monophosphate, and glycogen synthase kinase 3 in the central nervous system (CNS) [10].

Lithium decreases the concentration of inositol monophosphate, leading to impaired intracellular conduction and mood stabilization in patients with bipolar affective disorder [10]. On the other hand, lithium inhibits glycogen synthase kinase 3, an enzyme that exerts multidomain effects on the signaling pathways involved in energy metabolism, neuroplasticity, and the protection of neuronal structures. At the CNS level, it has been shown to induce serotonin release in the hippocampus [11]. Similarly, it decreases neuronal responsiveness to neurotransmitters by blunting the function of adenylate cyclase and G proteins, which are essential for opening ion channels [12]. Additionally, lithium has been shown to decrease norepinephrine and dopamine release from nerve terminals and may transiently increase serotonin release, which may explain its mood-stabilizing properties [10].

Absorption

Lithium is rapidly and almost entirely absorbed from the gastrointestinal tract after oral administration, reaching maximum plasma concentrations between 2 and 4 hours. The therapeutic range is very narrow, with serum lithium [Li⁺] concentrations generally between 0.6 and 1.3 mmol/L, being sensitive to minimal changes in renal and thyroid function [6]. The administration of a dose of lithium with intervals of 24 hours reduces kidney damage by up to 20% [13, 14]. In cases of acute poisoning, it can take more than 12 hours to reach its maximum serum concentration [15].

Distribution

Lithium is a small cation; it is widely distributed in the extracellular fluid and is almost not protein-bound. However, it has the potential to gradually accumulate in tissues, with a volume of distribution between 0.7 and 0.9 L/kg, which is lower in the population group of older adults with lower body mass and less total body water. Once the lithium reaches a stable state, the concentrations between the central nervous system and the kidneys have 40 to 50% of the total lithium content, and the rest is at the blood level.

Elimination

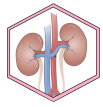
More than 95% of a single dose of lithium is eliminated primarily via the kidneys, with a half-life of 24 hours; in young people, the elimination is in the range of 12 to 18 hours, and in geriatric patients, it is 36 hours due to the lower estimated glomerular filtration rate (eGFR) that occurs after 60 years of age. After discontinuing the drug, a rapid phase of renal clearance is promoted, followed by a slow phase of up to 14 days. Despite being freely filtered, its reabsorption at the level of the proximal convoluted tubule is greater than 60%, competing with the reabsorption of sodium, which in conditions of dehydration or use of diuretics can cause an increase in serum concentration again. A small percentage of excretion of 1% occurs in feces and 4 to 5% in sweat [13].

Clinical manifestations

The clinical presentation of patients with lithium poisoning tends to be heterogeneous, from asymptomatic to severe toxicity, due to the exposure time and the different supratherapeutic plasma lithium concentration levels (Table 1).

Table 1. Manifestations of lithium poisoning by systems.

System	Manifestation
Cardiovascular	Sinus bradycardia, QT interval prolongation, ST-segment elevation, and arrhythmias [16].
Neurological	Confusion, agitation, neuromuscular excitability, seizures, nonconvulsive status epilepticus, and encephalopathy [9].
Gastrointestinal	Nausea, vomiting, and diarrhea [17].



Regarding severity classification for chronic patients, Hansen and Amdisen developed the first system in 1978 [18] (Table 2) [19]. However, acute poisoning during chronic drug use is the most common clinical situation [5].

Table 2. The link between severity and chronic plasma lithium concentrations.

Plasma lithium concentration.	Severity (Hansen and Amdisen classification)
1.5-2.5 mmol/L	Grade I (mild): nausea, vomiting, ataxia, muscle weakness, tremor, hyperreflexia
2.5-3.5 mmol/L	Grade II (moderate): rigidity, hypertonia, stupor, hypotension
>3.5 mmol/L	Grade III (severe) Seizures, myoclonus, coma, hemodynamic collapse.

Diagnosis

There are no clinical criteria for identifying patients with acute poisoning, and a high degree of clinical suspicion supported by laboratories and complementary diagnostic aids is necessary.

Leukocytosis is a primary characteristic; however, infections must be excluded [20].

- Serum electrolytes: Hyponatremia can perpetuate the tubular reabsorption of lithium [21].

Serum creatinine and blood urea nitrogen (BUN): Nitrogen measurements allow for the estimation of glomerular filtration, the establishment of the severity of intoxication, and the need for renal replacement therapy [22].

- Plasma lithium levels: They must be taken at the time of admission of the patient to the medical emergency department to confirm exposure to the drug and repeated 6 hours later to determine the maximum serum concentrations. The therapeutic range is narrow: during the initial stage, it should be between 0.6 and 1.2 mmol/L, and for prevention during the chronic phase of treatment, it should be kept between 0.4 and 1 mmol/L [10]. Early initiation of renal replacement therapy is determined based on its concentration in the blood. Serum concentrations have a more significant relationship with clinical signs in patients with chronic toxicity since the drug has reached a stable volume of distribution, which explains why some patients with acute poisoning may have average plasma concentrations unrelated to the clinical findings of toxicity [23, 24].

- Electrocardiogram: careful search for findings such as sinus bradycardia, QT interval prolongation, and ST segment elevation [16].

- Neuroimaging: Neuroimaging is helpful in scenarios where the diagnosis is confusing since it allows for evaluating differential diagnoses [25].

Treatment

There is no antidote for lithium poisoning [26, 27]. To reduce plasma concentrations, the use of lithium should be discontinued, as well as all medicines that can perpetuate its accumulation, such as diuretics [28, 29].

- Given the neurotoxic involvement, it is essential to evaluate the airway and determine if it is necessary to secure it through orotracheal intubation, avoiding drugs that lower the seizure threshold [30].

- Intestinal irrigation with polyethylene glycol may be helpful in lithium ingestion of less than one hour of evolution [31, 32].

- It is essential to correct secondary volume depletion and ensure adequate diuresis by avoiding forced diuresis with diuretics [29]. Some authors suggest using 0.9% saline, with the theoretical benefit secondary to additional tubular sodium loading promoting renal lithium excretion [33]. Conversely, some guidelines advocate using balanced solutions, such as lactated Ringers, to avoid hyperchloremic metabolic acidosis.

Extracorporeal treatment and renal replacement support

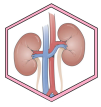
Lithium is a metal with a molecular size of 6.9 Da and a distribution volume of 0.6 to 0.9 L/kg, with low binding to plasma proteins and little endogenous clearance [34]. Its supratherapeutic levels cause high morbidity and mortality, which is why it is classified as a true dialysis emergency [35, 36]. In patients with normal renal function, the renal clearance of lithium is 10 to 25 ml/min; when intermittent hemodialysis is performed, clearance increases up to 170 ml/min, unlike other modalities, such as continuous renal replacement therapy, with an average clearance of 43 ml/min. Hence, the hemodialysis modality is the main route for removing the drug. Extended hemodialysis is recommended, with a duration of 6 to 12 hours, since studies have shown that this time can reduce circulating values within a therapeutic range and achieve serum values below one mEq/L [37, 38].

Due to the high intracellular lithium concentration, frequent rebounds can occur after hemodialysis due to redistributing its intracellular concentrations [6], so extended daily sessions are indicated [39]. Although continuous renal support therapies could be an adequate strategy for patients with hypotension and hemodynamic instability, studies suggest that this group of patients benefits the most from hemodialytic treatment and that these variables are not a contraindication to it [34, 38, 40].

The recommendations for the initiation of renal replacement therapy treatment were stipulated in 2015 by the American Society for the Extracorporeal Treatment of Poisoning (EXTRIP), which proposes the following indications (Table 3) [41].

Table 3. EXTRIP (Extracorporeal Treatments in Poisoning) recommends hemodialysis for lithium poisoning [41].

Plasma lithium concentration.	Grade of recommendation
Severe poisoning: hypotension, cardiopulmonary collapse, rigidity, myoclonus, seizures, coma, and stupor.	1D
Compromised renal function (eGFR < 45 mL/min/1.73 m ²) and lithium levels > 4.0 mEq/L	1D
Decreased level of consciousness (Glasgow coma scale < 15)	1D
Threatening arrhythmias	1D
Serum lithium >5 mmol/L	2D
Confusion	2D
The expected time to obtain serum lithium values < 1.0 mEq/L with optimal management is >36 hours	2D



The EXTRIP criteria described above are broad; therefore, strategies should be sought to select specific subgroups of patients who benefit from these supportive therapies. Future modifications might define these patient subpopulations [37]. However, most acute and chronic poisonings do not require hemodialysis. However, this intervention could shorten the hospital stay in patients with high toxin concentrations, as a recent publication shows [37]. In a study by Buckley et al., the nomogram accurately predicted the drop in lithium concentration for chronic poisoning, evidencing the use of hemodialysis guidance recommendations suggested by the EXTRIP criteria [37].

Currently, insufficient clinical evidence supports other therapies, such as hemoperfusion [28].

Long-term sequelae

Neurological

Syndrome of irreversible lithium neurotoxicity (SILENT) groups the development of prolonged neuropsychiatric and neurological symptoms following lithium toxicity. Manifestations include dysarthria, dysphagia, ataxia, nystagmus, choreoathetosis, myopathy, blindness, visuospatial deficits, and poor executive skills and memory [42, 43].

Renal

Patients chronically treated with lithium have a low risk of developing secondary tubulointerstitial nephropathy, leading to nephrogenic diabetes insipidus [44]. Regarding the risk of progression to chronic kidney disease, the development of this complication is rare [45].

Cardiovascular

electrocardiographic abnormalities due to flattening of the T wave, sinus bradycardia, and QT interval prolongation have been reported in the literature [16].

Conclusion

For many years, lithium has remained the primary agent in managing bipolar affective disorder. However, given its narrow therapeutic range, it requires strict control. Lithium poisoning is an entity with high morbidity and mortality. In many cases, this can be preventable with adequate follow-up, periodic taking of lithium from patients under this treatment, and insufficient education and information about its adverse effects so that they can be vigilant in case they appear. Early identification of symptoms can significantly impact the short-term, medium- and long-term prognosis. Carrying out adequate treatment is the best tool to avoid irreversible complications derived from this type

of poisoning, so it is essential to be clear at a critical moment when to act and especially when to start renal replacement therapy since it continues to be the best therapeutic option in severe poisoning given its high efficacy.

Abbreviations

EXTRIP: Extracorporeal treatments in poisoning.
GFR: glomerular filtration rate.

Supplementary information

Supplementary materials have not been declared.

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Author contributions

Jorge Rico Fontalvo: Conceptualization, Data Curation, Formal Analysis, Fundraising, Research, Methodology, Project Management, Resources, Software, Writing – original draft.

Maria Ximena Cardona Blanco: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition.

Rodrigo Daza-Arnedo: Methodology, validation, supervision, writing: Review and edition.

Liseth Paola Sierra Torres: Formal Analysis, Research, Methodology, Writing.

Juan Carlos Marrugo Yunda: Formal Analysis, Research, Methodology, Writing.

Tomas Rodriguez-Yanez: Formal Analysis, Research, Methodology, Writing.

Maria Raad Sarabia: Formal Analysis, Research, Methodology, Writing.

Elba Vanesa Villavicencio Ceron: Formal Analysis, Research, Methodology, Writing.

All authors read and approved the final version of the manuscript.

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Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable scholarly request.

Statements

Ethics committee approval and consent to participate

Does not apply.

Consent for publication

It does not apply when images or photographs of the physical examination or patients' X-rays/CT/MRI are not published.

Conflicts of interest

The authors report having no conflicts of interest.

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