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Review Article

Lithium Poisoning Update in Diagnosis and Treatment

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Abstract: *Introduction*: Lithium has been used over time in the treatment of psychiatric pathologies, mainly the bipolar spectrum, however, the narrow therapeutic range generates a high incidence of poisoning by this metal, with a very heterogeneous clinical presentation of toxicity which will depend on two factors: the time of evolution, if it is acute or chronic, and the serum levels, ranging from gastrointestinal symptoms to severe neurological compromise. As of today, there is no specific antidote for lithium, so intermittent hemodialysis is the strategy of choice for the intoxicated patient. *Objectives*: To describe the available and relevant literature on the management of Lithium poisoning. *Methodology*: A search was performed with the MeSH terms "Lithium, Renal Dialysis, Poisoning, Toxicity, Acute kidney injury" in the ClinicalKey, PubMed and Ovid databases search engines, finding 156 results, of which 47 were used to develop this manuscript. *Conclusions*: Lithium poisoning is frequent due to its narrow therapeutic margin, so serum lithium levels should be monitored in patients medicated with it. Today there is no specific antidote, so renal replacement therapy is the best therapeutic option for lithium poisoning, demonstrating high efficiency, especially in cases of marked neurotoxicity. It is necessary to assess the need to initiate timely management in order to achieve a rapid clearance of the drug and decrease the rate of complications and mortality.

Keywords: Lithium, Renal Dialysis, Poisoning, Toxicity, Acute Kidney Injury (MeSH)

1. Introduction

Lithium, a metal and monovalent cation, with characteristics similar to sodium and potassium [1, 2] has been historically used in the treatment of psychiatric disorders such as depression and mania [3]. Its history dates back to the 19th century, where it was administered in the form of a tonic to patients with conduct disorders; A long time later, in 1949, John FJ Cade described the "anti-mania" molecular mechanisms of Lithium and in the 1970s, it was approved by the FDA for the treatment of disorders in the bipolar spectrum. [4]

Despite extensive medical experience with the use of lithium as a medicine, its exact mechanism of action is not well defined, however, its therapeutic effect is thought to be due to impaired sodium transport and catecholamine metabolism due to at the neuronal level [5, 6], this is done through two intracellular signaling pathways: inhibition of inositol monophosphate and inhibition of glycogen synthase kinase-3, which generates a lower capacity of alpha adrenergic response, decreased adenylate cyclase and G protein activity [7]. Due to its similarity to other cations such as sodium and potassium, it can cause alteration of the membrane action potential [8] and, on the other hand, an increase in the release of serotonin in the hippocampus has been described [7].

The pharmacokinetics of lithium depends on the presentation used. In the case of citrate and lithium carbonate, they are rapidly absorbed after their administration via the gastrointestinal route, however the fastest absorption occurs in the form of a solution that does so in less than 60 minutes [5, 7, 9]. There are also regular-release and prolonged-release presentations, which have an average absorption time of 1-3 hours and 3-6 hours, respectively [5]. The bioavailability in general is good, ranging from 60-95% depending on the presentation; and its "anti-mania" effect begins to be evident between days 5 and 7, achieving clinical effectiveness between the second and third week of treatment [10].

The body distribution is wide after its absorption, including tissues such as thyroid, bones and brain; plasma protein binding is nil, and it is excreted almost entirely by the kidneys without having undergone endogenous metabolism [5]. The renal clearance of lithium varies between 10 to 40 ml / minute, which decreases in advanced ages to 15 ml / minute, increasing the half-life up to 58 hours [11].

2. Methodology

A search was performed with the MeSH terms "Lithium, Renal Dialysis, Poisoning, Toxicity, Acute kidney injury" in the ClinicalKey, PubMed and Ovid databases search engines, finding 156 results, of which 47 were used to develop this manuscript.

3. Lithium Poisoning

Lithium is considered the first therapeutic agent for bipolar disorder, however, the clinical benefits should be evaluated against the high frequency of adverse effects and its extremely narrow therapeutic range with values ranging between 0.7 and 1.2 mEq / L [1]. Changes in its dosage or conditions that worsen its excretion, such as acute or chronic kidney disease, can generate increased serum levels and generate toxicity [7]. However, other conditions may also vary the literacy, such as dehydration from vomiting or diarrhea, fever, excessive exercise, excessive sweating, low sodium diet and congestive heart failure (the latter increases renal reabsorption of lithium) [7, 12, 13].

The multiple drug interactions (diuretics, ACE inhibitors, ARBs, non-steroidal anti-inflammatory drugs, antipsychotics, neuromuscular blockers, calcium channel antagonists), also configure a trigger for the development of lithium poisoning [14]. Table 1 summarizes the pharmacological and non-pharmacological factors, which cause changes in the litemia and increase the risk of toxicity.

Table 1. *Risk Factors for Lithium Poisoning.*

Advanced age.
Dehydration: Low water intake, vomiting, diarrhea, intense exercise.
Increased callous losses: fever.
Renal insufficiency.
Infections.
Medications: Diuretics (ASA, thiazides, aldosterone antagonists), ACE INHIBITORS, ARBs, CA, NSAIDs, antidepressants, antipsychotics, neuromuscular blockers.

ACE inhibitors: Angiotensin-converting enzyme inhibitors; ARB II: Angiotensin II receptor blockers; CA: Calcium channel antagonists; NSAIDs: Non-steroidal anti-inflammatory drugs.

3.1. Clinical Manifestations and Initial Evaluation

The clinical presentation of lithium poisoning is very heterogeneous, and will depend on two factors: the time of evolution, whether it is acute or chronic, and the serum levels as shown in Table 2 [7]. Based on this, there are three patterns of lithium poisoning: acute in patients who have previously been taking lithium, acute in patients who have not been previously medicated, and chronic poisoning.

In acute poisoning in individuals without prior exposure, given the pharmacokinetic properties of the drug and the slow rate of distribution to the tissues, the maximum plasma lithium concentration is not high enough to generate severe poisoning unless actively retained in the intracellular space. Acute poisoning in patients who were treated with lithium therapy occurs in cases of overdose or alteration in endogenous clearance, at this point the clinical manifestations depend on the previous circulating concentration of the drug, in addition to the amount taken acutely and the excretion rate. Finally, chronic poisoning occurs when the intake of lithium exceeds the elimination in a chronic way, the symptoms occur over days or weeks and are mostly neurological because the long exposure time allows the accumulation of the drug at the neuronal level and its passage through the blood-brain barrier. [15]

The initial symptoms and the main reason for consultation in cases of poisoning are gastrointestinal symptoms such as

nausea, vomiting and diarrhea; however, patients may debut with malignant cardiac arrhythmias due to QTc prolongation, or consult with symptomatic bradycardia [15, 16]. Lithium cardiotoxicity, although little reported, can vary from arrhythmias and cardiomyopathies to myocardial infarction [16].

Neurological findings in lithium poisoning are late and predominate in chronic poisoning as mentioned above. They can range from the presence of mild symptoms such as drowsiness, confusion, mild alteration of the state of consciousness to severe symptoms such as muscle excitability (tremors, fasciculations, myoclonus) and others that involve cerebellar involvement such as ataxia, dysarthria and dysphagia; in severe cases, seizures, encephalopathy, and death can occur.

Renal compromise, which occurs most frequently in patients with chronic poisoning, is characterized by tubulointerstitial nephritis and the predominant symptoms are compatible with nephrogenic diabetes insipidus (polyuria, polydipsia) that lead to volume depletion and activation of the renin system angiotensin aldosterone, which in turn leads to increased reabsorption of lithium [18].

Table 2. *Clinical presentation according of serum lithium levels.*

Lithium concentration (mEq/L)	Clinical presentation
1.5-2.5	Nausea, vomiting, lethargy, tremor, and fatigue
2.5-3.5	Confusion, agitation, delirium, tachycardia, and hypertonia
> 3,5	Coma, seizures, hyperthermia, and hypotension

The initial evaluation of the patient with lithium poisoning includes cardiac and electrocardiographic monitoring [19]; blood biochemistry studies such as glycemia, creatinine, BUN, electrolytes, thyroid stimulating hormone, uroanalysis [20], constant evaluation of vital signs and state of consciousness, arterial blood gas measurement for evaluation of acid base and oxygenation state, approach the airway if necessary and monitor urinary output [7].

3.2. Effects of Lithium at Renal Level

Half of the patients treated with lithium can present polyuria days to weeks after starting their intake. Of this group of patients, about 20% develop nephrogenic diabetes insipidus (NDI) [21], generating loss of the ability to concentrate urine due to resistance to the effect of vasopressin [22-24].

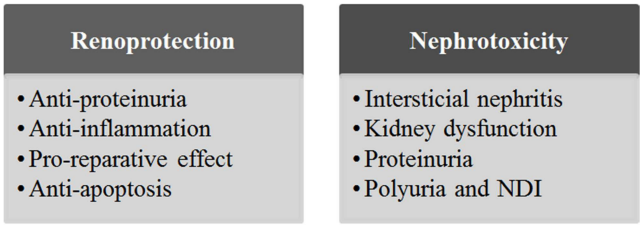
The main consequences of NDI development include hypovolemia, hypernatremia, hyperchloremic metabolic acidosis, and distal renal tubular acidosis [21].

The mechanisms involved in the formation of NDI are explained by the entry of lithium into the epithelium of the collecting tubule, starting from the ENaC channels [25]. Additionally, in animal models, a decrease in the expression of aquaporin-2 receptors has been demonstrated after several days of lithium administration, causing polyuria and poor ability to concentrate urine; this disorder was mitigated with the use of amiloride [26].

Other processes involved in the development of NDI are the increased levels of cyclooxygenase-2 and prostaglandin E in renal interstitial cells [21]; blocking the activity of glycogen synthase kinase (GSK-3), which participates in the regulation of vasopressin and its interaction with the aquaporin-2 receptor in the collecting tubule [27]. The mechanism of decreased vasopressin activity is multifactorial, lithium is able to compete with magnesium ions, which inhibits vasopressin-sensitive adenyl cyclase [22].

Fortunately, polyuria and the development of NDI do not have an aggressive behavior and improve after the suspension of lithium [21, 28]. However, chronic kidney disease, proteinuria, and nephrotoxicity have been reported in patients with prolonged use of lithium [29].

In contrast to the nephrotoxic effects of lithium, its administration in therapeutic ranges has renoprotective effects, as shown in Figure 1 [21]. The mechanism involved in renal protection appears to be associated with inhibition of GSK-3 and decreased apoptosis of tubular cells [30], increased proliferative factors in the renal tubules, including cyclin D1, c-Myc and the hypoxia-inducible factor-1α [31]. The easiest way to compensate for this balance between benefit and harm is to reduce the doses and administer them for short periods of time; since high doses and prolonged therapies are undoubtedly risk factors strongly associated with nephrotoxicity [21].



NDI: Nephogenic diabetic insipidus.

Figure 1. *Paradox between renoprotection and lithium nephrotoxicity.*

3.3. Lithium Poison Management

Although lithium poisoning is not a frequent visit to the emergency services, it does have a high mortality rate, so its approach must be timely and oriented according to evolution and clinical manifestations. It is important to bear in mind that when toxic levels are reached, the clinical manifestations may appear late, so the symptoms do not usually reflect the magnitude of the intoxication and it is always necessary to have lithium levels to establish adequate treatment [32].

Nowadays there is no known antidote in the case of lithium poisoning, therefore, its management is based on two fundamental pillars: firstly, to decrease circulating levels of lithium and, secondly, to correct hydroelectrolytic disorders to decrease multi-organ involvement [33]. As the central

nervous system is one of the main organs involved, the compromise of the state of consciousness and the need to protect the airway must be evaluated; in addition, all medications that predispose to lithium poisoning should be discontinued immediately [34].

On the other hand, and in the context of volume depletion secondary to NDI, the administration of 0.9% saline is indicated to improve renal perfusion, increase renal excretion of lithium and, in addition, it has a theoretical benefit since it reduces tubular reabsorption of lithium by providing an additional sodium charge [35]. The administration of diuretics is contraindicated since the volume status worsens and some diuretics (such as thiazide and loop diuretics) aggravate hydro-electrolyte disorders and may increase the reabsorption of lithium [36].

Gastrointestinal decontamination, the use of gastric lavage and polystyrene resins remain in controversy, various studies support its use only in cases of acute poisoning and by delayed-release presentations, especially in those cases where renal replacement therapy is not possible [37, 38], however, additional studies are still required to approve its use in other clinical stages such as moderate to severe poisonings.

3.4. Renal Support Therapies in Lithium Poisoning

The clinical characteristics of the drug, for example, its small molecular weight, low binding to plasma proteins, low volume of distribution, and poor endogenous clearance, make hemodialysis the therapeutic strategy of greatest evidence and use in the context of lithium poisoning [39, 40]. The goals of hemodialysis are to decrease high concentrations of lithium in toxic behaviors, such as the central nervous system, and to favor a concentration gradient that allows lithium to diffuse into plasma for its subsequent elimination [41].

High-efficiency hemodialysis leads to a lithium clearance up to ten times higher than endogenous clearance, reaching up to 100-120 ml / min [42] and its indications, although they are still controversial because they are based on consensus of experts and small cohort studies were summarized by EXTRIP (Extracorporeal Treaments in Poisoning) in 2015 as shown in Table 3 [43].

Prolonged hemodialysis (PHD) is the extracorporeal therapy of choice in lithium poisoning, since in addition to being the best cost-benefit method, it is more efficiently adapted to eliminate small molecules such as lithium [43]. The recommended duration of therapy is 6-8 hours as it is considered sufficient time to decrease the circulating values to therapeutic ranges and should be suspended once the serum lithium values are less than 1 mEq / Lt or the margin of time mentioned above. The existing evidence regarding the other modalities is little or nil, however, it is accepted as an alternative to PHD to perform continuous renal replacement therapy (CRRT) in case the former is not available because with CRRT there is a plasma clearance of the lowest lithium levels compared to PHD and, in this case, it is recommended that its duration be approximately 24 hours [43, 44]. There is insufficient evidence to recommend other extracorporeal therapy modalities such as low-efficiency sustained dialysis, plasma exchange, or charcoal hemoperfusion [45].

Table 3. *Recommendations for extracorporeal treatment for lithium poisoning.*

RECOMMENDED EXTRACORPORE TREATMENT
Severe lithium poisoning (stupor, stiffness, hypertonia, hypotension, coma, cardiovascular collapse)
Compromised renal function (GFR <45ml / min) and Lithium concentrations greater than 4.0 mEq / Lt
Compromise of state of consciousness (Glasgow less than 15)
Seizures
Arrhythmias that compromise life
SUGGESTED EXTRACORPORE TREATMENT
Lithium> 5 mEq / Lt
Confusión
Lithium> 1 mEq / Lt with optimal therapy over 36 hours

During renal replacement therapy, the consideration must be taken into account that lithium clears more slowly from the tissues than from plasma, so it is common for a phenomenon known as "rebound" to occur, this consists of increased lithium levels after cessation of renal replacement therapy [36]. This phenomenon may also occur in those patients in whom there is persistent absorption by the gastrointestinal tract. The rebound phenomenon commonly occurs in those cases where maximum efficiency modalities are used in the following 6-12 hours after the initial therapy and are not associated with acute symptoms of intoxication since lithium moves away from the toxic compartment. In sporadic cases in which the rebound phenomenon generates clinical symptoms, it has been associated with initial intoxication from prolonged-release forms [46]; it is in this clinical setting that the consensus of experts recommends the use of additional sessions of PHD or CRRT [43].

Another therapy that has been used for the management of lithium poisoning is hemoperfusion, however, no benefit has been demonstrated with the use of this treatment modality in patients poisoned with lithium. More clinical trials of this therapy are necessary to recommend its routine use [47].

4. Conclusions

Over the years, lithium has established itself as the first-line agent for bipolar affective disorder and other neuropsychiatric pathologies, however its use is highly restricted due to the narrow therapeutic range and the high risk of patients who are under medication. Monitoring of plasma lithium levels should be frequent in medicated patients and symptoms of mild, moderate or severe poisoning always need medical attention. Renal replacement therapy is the best therapeutic option for lithium poisoning given its molecular characteristics, demonstrating high efficiency, especially in cases where there is marked neurotoxicity. In all cases of intoxication, it is necessary to evaluate, in light of the recommendations, the need to start renal replacement therapy in a timely manner in order to rapidly clear the drug and decrease future complications and the high mortality rate.

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