Review Article

Lithium Toxicity: Role of Hemodialysis

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Abstract : *Lithium is one of the most frequently used drugs for treating mood disorders. It is used for both prophylaxis and treatment of bipolar affective disorder. It should be cautiously prescribed and used only when clinically indicated because of narrow therapeutic index and significant toxicity. One of the most alarming and potentially serious complications of lithium carbonate therapy is central nervous system toxicity. It is difficult to recognize early toxicity since signs and symptoms of mild lithium toxicity may be mistaken for other diagnoses. Severe toxicity affects predominantly Central Nervous System and Cardiovascular System and may prove to be fatal. Such cases require early recognition and intervention to prevent any irreversible organ damage or death. Hemodialysis remains the mainstay of treatment in severe lithium toxicity. The decision to start hemodialysis should rely on a combination of clinical features of toxicity, duration of exposure to lithium and serial lithium levels. The current effort is to analyze why lithium toxicity is common, how to recognize it early and intervene in time. Available guidelines for hemodialysis in such cases have been reviewed and discussed.*

Key Words: Lithium Toxicity, hemodialysis, early intervention

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INTRODUCTION

Since John F.J. Cade's observation of antimanic effects of lithium in 1949, it is considered the first choice drug for treating bipolar affective disorders. It is widely used for prophylaxis and treatment of mania and depression in bipolar affective disorder where it reduces number and severity of relapses.[1,2] Lithium augmentation of anti-depressants is useful in treatment-resistant unipolar depression. It is also useful in conditions like schizoaffective disorder, alcoholism, or aggressive behavior when a significant affective component coexists. Lithium has proven to be useful in the prophylaxis of cluster headaches and in ameliorating chemotherapy-induced neutropenia.[3]

Despite its usefulness, lithium is a double-edged sword. Its safe therapeutic range is so narrow that it seems toxicity is inevitable, it was estimated that 75%-90% of patients maintained on lithium therapy were found to have signs and symptoms of toxicity at some time.[4] Patients on long term therapy are at greater risk of manifesting severe lithium toxicity. Severe neurotoxicity represents the most significant manifestations of toxicity.[5] Fatal toxicity has been reported in 15% of the cases with severe lithium toxicity.[6] Levels of toxicity whether mild, moderate or severe are based on serum lithium levels in chronically treated patients, which is a fair guide to intracellular lithium levels.[7] Hemodialysis is by far the choice of treatment in severe lithium toxicity.[8] There are guidelines for the management

of lithium toxicity; however the indications for hemodialysis are not so clear.

Why lithium toxicity is common?

Lithium constitutes insignificant amount as a normal constituent of body (< 0.2 mEq/L) and majority comes from intake of lithium as lithium carbonate. Once inside the body, lithium is substituted for sodium/potassium on several transport proteins for its movement in or out of the cells. The pathways for transporting lithium out of the cells are more limited than those moving lithium inside the cells, resulting in lithium accumulation intracellularly over time.[9] This might be the reason for its prolonged half-life in patients on chronic lithium therapy. Single dose administered lithium will have elimination half-life from the peripheral circulation of about 7-20 hrs, which goes up to 60 hrs during chronic lithium treatment.[7,8,10] The estimated elimination half-life for lithium in red blood cells and cerebrospinal fluid is much slower during toxicity, reported to be 43.7 and 67.5 hours respectively.[11] Such slow elimination from the cells could explain occurrence of neurotoxicity despite declining lithium levels in peripheral circulation with hemodialysis and may underlie non-resolution of the neurological abnormalities in the initial period of toxicity.

Renal lithium clearance in normal individuals is 10-40 ml/min.[12-14] This is proportional to glomerular filtration rate, and factors affecting it will have significant effect on the clearance of lithium. Lithium at toxic levels is thought to inhibit its own excretion. During lithium intoxication its renal clearance decreases to as low as 5 ml/min to 0.9 ml/min. This self-inhibiting effect is said to be responsible for the development of toxicity so rapidly once the lithium has risen beyond a critical point.[7,15] If it were so, then identifying such a critical level would help us in deciding exactly when to intervene during lithium toxicity.

Signs and symptoms of mild lithium toxicity such as gastrointestinal disturbances, tremors, fatigue, apathy and weakness may be mistaken for many other diagnoses. Determining whether the patient is having side effect of lithium at therapeutic level of serum lithium becomes a challenge. Diagnosis rests on high degree of clinical suspicion. Though some have suggested use of EEG, wherein generalized slowing of EEG compared to base line might support toxicity in doubtful cases, but this seems too non-specific.[16]

Levels of toxicity whether mild, moderate or severe are based on serum lithium levels in chronically treated patients, which is a fair guide to intracellular lithium levels[7] , but many authors recommend placing greater emphasis on patient's clinical status for toxicity grading as there is no clear cut relationship between serum lithium levels, severity of symptoms and patient's prognosis.[6,16]

Who are more prone to toxicity?

Of clear importance are conditions that decrease renal clearance of lithium. Following filtration, 80% of lithium is reabsorbed in the proximal tubules, along with water and sodium. All conditions that decrease the glomerular filtration rate or increase proximal reabsorption may induce lithium toxicity. Longer duration of exposure to increased doses of lithium, use of sustained release preparation of lithium, degree of elevation of serum lithium level, older age, preexisting brain damage and suffering from schizophrenia predispose to lithium toxicity and any factors influencing water and electrolyte metabolism/kidney disease, salt restriction, use of thiazide diuretics, non-steroidal anti-inflammatory drugs (NSAIDS), and

angiotensin-converting enzyme inhibitors (ACE inhibitors), tilt the balance in unfavorable way.[17,18] Presence of higher rates of medical co-morbidities like NIDDM, hyperglycemic ketoacidosis, hypertension and the drugs used for their treatment in chronically treated psychiatric patients and concurrent use of antipsychotics and anticonvulsants (eg, carbamazepine), puts them at increased risk for lithium toxicity.[19]

Manifestations of lithium toxicity

Acute lithium intoxication is a frequent complication of chronic lithium therapy. It mimics physical illnesses seemingly unrelated to lithium therapy and mood disorder. Lithium intoxication can manifest as neurotoxicity, cardiotoxicity, or nephrotoxicity. Gastrointestinal side effects commonly appear during commencement of therapy; however nausea, vomiting and diarrhea may be the early symptoms of lithium toxicity.[20] Neurological manifestations of toxicity are the most frequent. Lithium neurotoxicity in early stages can manifest as nonspecific neurological and psychological symptoms, such as decreased alertness, weakness, slurred speech, tremor, restlessness, apathy, muscular rigidity and fasciculation. Warning symptoms of cardiotoxicity include dizziness, syncope and other changes in cardiac function. Nephrotoxicity may present as impairment of urinary concentrating ability and polyuria or polydipsia. Even subtle changes in mental status or central nervous system, cardiac, or renal functioning should be investigated to identify or rule out lithium intoxication.[21]

Symptoms of early toxicity might progress to severe intoxication. In severe neurotoxocity, confusion worsens into stupor; tremor can become more severe; spontaneous or latent twitching movements of the limbs, body, and head can appear; and seizures and coma sometimes develop. Worsening cardiotoxicity can manifest itself as bradycardia, sick sinus syndrome, ventricular and atrial arrhythmias, bundle branch block, or myocarditis.[6,22-26] Severe cardiotoxicity may cause death or require cardiac pacing. Severe nephrotoxicity may lead to renal insufficiency or renal failure and can result in renal damage or even death.[8-9,24,27,28]

A past or present episode of lithium intoxication is one of the important risk factors for renal failure in patients maintained on lithium.[29] Some view lithium to have direct nephrotoxic effect.[30] Whether renal impairment poses risk for lithium toxicity, is not clear while reverse is true so, timely reduction of high lithium dose during toxicity is priority and can be achieved promptly by hemodialysis. Reported morbidity and mortality due to complications arising out of lithium toxicity, is around 10% - 12.5%.[21] Fatal dose with acute consumption is said to be 6 gm only. It is probably avoided as a suicidal agent due to unawareness, unavailability or because it doesn't cause instantaneous death, rather death is secondary to its complications, than to lithium primarily.

Management

As a preventive measure proper selection of patients, proper instructions when starting lithium, frequent monitoring which includes laboratory investigations and assessment for co-morbidities like hypertension, diabetes and the drugs prescribed for these conditions which may have interaction with lithium pharma-cokinetics.

Management of lithium intoxication involves stopping lithium, giving gastric lavage with

polythene glycol or bowel irrigation especially if it is sustained release lithium preparation. [31] Various modalities for lithium removal exist like, forced alkaline diuresis, peritoneal dialysis, hemodialysis, and continuous arteriovenous hemofiltration. In forced alkaline diuresis there is risk of hyponatremia and volume overload[6,32] and with peritoneal dialysis there is need for anticoagulation and there is a high risk of infection. Saline diuresis was found to be an ineffective method for lithium elimination.[6] An effective oral treatment adjunct is the administration of sodium polystyrene sulphate, which can prevent lithium absorption when used early after ingestion. Sodium polystyrene sulfate has been shown in an animal model to increase lithium elimination even when lithium was given parenterally.[33-35] Even when used late after acute lithium overdose it has been reported to be beneficial, and it may well have a place in the treatment of chronic lithium overdose and poisoning caused by sustained-release preparations.[18]

Role of hemodialysis

Lithium is ideally suited to removal by hemodialysis, with small atomic weight and negligible protein binding and it is one of the most readily dialyzable toxins. Existing recommendation are based on patients who developed acute toxicity on chronic lithium therapy. Some investigators stress on serum lithium levels, while others recommend hemodialysis going by the clinical status of the patient. Hemodialysis has been sole modality consistently showing higher rate of lithium removal (Table 1) and expediting the period of exposure to lithium load during toxicity. During lithium toxicity not intervening or intervening with too many drugs might be precarious to already disturbed homeostasis maintaining fluid and electrolyte balance. There are reports of successful conservative management even at serum lithium levels as high as 4.5-8.0 mEq/L, but such instances are being case reports only.[6,36-38]

Table 1

Lithium Elimination

Mode	Lithium clearance* (ml/min)
Renal excretion	10-40
Forced diuresis	0.9-39
Peritoneal dialysis	9-15
Hemodialysis	70-170

*At blood flow of 126-250 ml/min.

Following is the summary of existing recommendations/guidelines including both serum lithium level and clinical status. This is an attempt to simplify existing various opinions and cut-off levels be presumed as arbitrary.

1. At serum lithium level >4.5 mEq/L and irrespective of clinical status go for hemodialysis.[4,39-44]
2. At serum lithium levels of 3.5-4.5 mEq/L and associated with any signs of severe cardiac, neurological or renal impairment, one can opt for hemodialysis without waiting.[45] If it is associated with either moderate or mild clinical toxicity symptoms either one can go for hemodialysis or wait and watch for next 6 hrs. During this if serum lithium fails to decrease, go for hemodialysis.[40,46,47]
3. At serum lithium levels of 2.5-3.5 mEq/L and severe clinical symptoms, one can opt for hemodialysis. If this serum level associated with moderate or mild toxicity symptoms, one can wait and watch as above or alternatively determining rate of elimination, if log scale of 3 consecutive serum lithium drawn at 3 hrly

interval predicts that lithium level concentration will not decrease below 0.6 mEq/L in less than 36 hrs, hemodialysis can be considered.[37,48]

4. Dialysis is rarely indicated in patients with lithium levels below 2.5 mEq/L. At serum lithium level <2.5 mEq/L and clinical presentation is of coma, convulsions, respiratory failure, deteriorating mental status or renal failure, then only hemodialysis is advisable.[45]

During dilemma or waiting period, conservative management is followed. If lithium level fails to decrease despite conservative therapy, whether due to continued GI absorption or diffusion of lithium from intracellular stores, then hemodialysis is advisable. If more lithium can be cleared by a single hemodialysis treatment than by the kidney in 24 hrs, hemodialysis is better choice compared to conservative management. Typically two sessions of hemodialysis are required and usual end point is aimed at below 1 mEq/L. There is risk of rebound following hemodialysis up to level of 85%-100% of predialysis level. This can be minimized by using bicarbonate dialysate instead of acetate dialysate,[45] and careful monitoring of serum level after hemodialysis.

CONCLUSIONS

Lithium will continue to be used in bipolar affective disorders as mood stabilizer and for many other conditions. Lithium toxicity may manifest in diverse forms, with symptoms of gastroenteritis to a severe multi-systemic involvement and particularly affecting neurological and cardiac functions. The best approach is of course the prevention. Early identification and management of dehydration, sodium depletion and judicious use of NSAIDS, diuretics and ACE inhibitors in patients on long term lithium therapy can prevent development of lithium toxicity. Increased awareness among physicians and psychiatrists and optimal use of hemodialysis, may help in preventing the mortality and irreversible sequelae in such cases. In cases of lithium toxicity wherever facilities exist hemodialysis can be used as an early intervention and is the specific antidote for lithium toxicity.

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