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Lithium Poisoning

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Abstract

Lithium is a commonly prescribed treatment for bipolar affective disorder. However, treatment is complicated by lithium's narrow therapeutic index and the influence of kidney function, both of which increase the risk of toxicity. Therefore, careful attention to dosing, monitoring, and titration is required. The cause of lithium poisoning influences treatment and 3 patterns are described: acute, acute-on-chronic, and chronic. Chronic poisoning is the most common etiology, is usually unintentional, and results from lithium intake exceeding elimination. This is most commonly due to impaired kidney function caused by volume depletion from lithium-induced nephrogenic diabetes insipidus or intercurrent illnesses and is also drug-induced. Lithium poisoning can affect multiple organs; however, the primary site of toxicity is the central nervous system and clinical manifestations vary from asymptomatic supratherapeutic drug concentrations to clinical toxicity such as confusion, ataxia, or seizures. Lithium poisoning has a low mortality rate; however, chronic lithium poisoning can require a prolonged hospital length of stay from impaired mobility and cognition and associated nosocomial complications. Persistent neurological deficits, in particular cerebellar, are described and the incidence and risk factors for its development are poorly understood, but it appears to be uncommon in uncomplicated acute poisoning. Lithium is readily dialyzable, and rationale support extracorporeal treatments to reduce the risk or the duration of toxicity in high-risk exposures. There is disagreement in the literature regarding factors that define patients most likely to benefit from treatments that enhance lithium elimination, including specific plasma lithium concentration thresholds. In the case of extracorporeal treatments, there are observational data in its favor, without evidence from randomized controlled trials (none have been performed), which may lead to conservative practices and potentially unnecessary interventions in some circumstances. More data are required to define the risk–benefit of extracorporeal treatments and their use (modality, duration) in the management of lithium poisoning.

Keywords

enhanced elimination, extracorporeal treatment, neurotoxicity, syndrome of irreversible lithium effectuated neurotoxicity, intermittent hemodialysis, continuous renal replacement therapy, sodium polystyrene sulfonate

Introduction

Lithium has been prescribed since the 1870s for a number of conditions including treatment of gout, depression, and as a salt substitute for heart failure. However, its use was curtailed because of its significant toxicity profile associated with inattention to dosing and monitoring. Cade[1] has been credited for the rediscovery of the mood stabilizing properties of lithium salts, and Baastrup[2] demonstrated its effectiveness. Since then, lithium has been used as a mood stabilizing agent.[3]

Despite evidence of clinical efficacy, its mechanism of action remains elusive but may reflect alterations in transduction pathways related to glutamate, inositol monophosphate, and glycogen synthase kinase 3 in the central nervous system (CNS). Lithium has been shown to decrease the release of noradrenaline and dopamine from nerve terminals and may also transiently increase the release of serotonin, which may account for its mood stabilizing properties.[4]

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Lithium has a very narrow therapeutic index, and clinical features of toxicity can be noted at plasma lithium concentrations close to the upper limit of the reference range for therapeutic concentrations. Lithium intoxication can occur due to an acute deliberate ingestion or be an unintended consequence of therapeutic misadventure due to various factors, which lead to chronic poisoning. Such factors include any of a number of drug interactions (see Box 1), prescribing or dispensing errors, intercurrent illnesses that impair renal function (gastroenteritis), or more chronic causes of volume depletion as seen in dehydration and lithium-induced nephrogenic diabetes insipidus. Symptomatic lithium poisoning is usually unintentional as shown in data published in the National Poison Data System Report.[7] Of the 6610 cases of documented lithium intoxication in 2013 across the United States, 1173 of these cases (18%) were the result of an intentional overdose.

Box 1. Drug Interactions That Can Increase Plasma Lithium Concentrations.

Reduce glomerular filtration rate (GFR)
- Nonsteroidal anti-inflammatory drugs (NSAIDS)
- Renin-angiotensin system inhibitors[5]

Promote renal tubular reabsorption
- Thiazide diuretics
- Spironolactone

Uncertain mechanism
- Calcium channel blockers (diltiazem, verapamil). Nifedipine has been shown to reduce lithium clearance when administered chronically[6]

Historically, lithium toxicity was associated with a significant mortality rate. Hansen and Amdisen[8] reviewed the literature and added their own patient experience. They reported that, prior to 1975, mortality ranged from 9% in patients who presented with toxicity from chronic poisonings to 25% in acute poisonings. These results probably overestimated mortality due to the presence of publication bias, and fortunately, recent estimates of mortality are much lower: 0% (Australia; retrospective single center series),[9] 0% (United Kingdom; Poison Control Center [PCC] telephone consultations),[10] 1.0% (Canada, PCC telephone consultations),[11] and 0.8% (United States; PCC telephone consultations).[7,12] Despite low mortality, lithium intoxication may require intensive management over several days and treatment decisions can be complex. There is also concern about the risk of permanent neurological sequelae, and it is postulated that by timely interventions such as fluid resuscitation and enhanced elimination, including the use of extracorporeal treatments (ECTRs), in selected patients, the duration of exposure of the brain to toxic lithium concentrations may be reduced.

Clinical Features of Lithium Toxicity

Influence of the Pattern of Exposure on Lithium Pharmacokinetics, and the Onset and Offset of Toxicity

Although lithium can eventually lead to multisystem toxicity, lithium's most important site of toxicity is the CNS. The risk of development of neurotoxicity is directly related to the pattern of exposure that led to the poisoning, which in turn reflects the pharmacokinetic properties of lithium. There are 3 patterns of lithium poisoning: acute, acute-on-chronic, and chronic, and these are discussed in detail below. The risk of neurotoxicity is lowest with acute poisoning and highest with chronic poisoning, owing to the differences in the opportunity for lithium to distribute to the intracellular space in the CNS, relative to the plasma concentration–time profile.

This phenomenon relates to the multicompartmental pharmacokinetic profile of lithium. Over a number of hours post-ingestion, lithium distributes into the whole body water. The rate at which it distributes in, and then out of, intracellular spaces is slow relative to the rate at which lithium is eliminated from the body. As a result, it takes time for lithium to accumulate in the intracellular space with chronic therapy but also for the concentration to decrease when lithium therapy is ceased (see Figure 1). The blood–brain barrier may additionally slow distribution into the brain. Because the intracellular concentration in the brain is considered the main site of toxicity of lithium, this is often referred to as the "toxic compartment."[14]

Acute poisoning is an overdose taken by a lithium-naive individual. Here, considering the compartmental pharmacokinetic properties of lithium and the slow rate of distribution to the intracellular space, the peak intracellular lithium concentration should not exceed the peak plasma lithium concentration, unless it is actively retained in the intracellular space (Figure 1).

Chronic poisoning occurs when lithium intake exceeds elimination on a chronic basis, usually weeks, and the range of factors that may induce this were discussed above.

Finally, acute-on-chronic poisoning occurs when an individual who is already taking lithium chronically takes an acute overdose. Here, the risk of neurotoxicity depends on the steady-state concentration prior to the overdose, the amount taken acutely, and the rate of elimination (kidney function).

The clinical implications of these principles, including the disconnection between plasma concentrations and clinical toxicity, will be discussed further.

Initial Manifestations

The initial manifestations of lithium poisoning are heterogeneous, ranging from an asymptomatic individual to one displaying signs of toxicity of varying severity (see Box 2). Important signs of neurotoxicity include confusion, ataxia/incoordination, seizures, and encephalopathy. In more severe cases, airway reflexes may be impaired leading to an increased risk of secondary complications such as aspiration pneumonitis.

The heterogeneity of initial manifestations largely reflects 2 pharmacokinetic variables: plasma lithium concentrations and duration of exposure to the supratherapeutic concentrations.

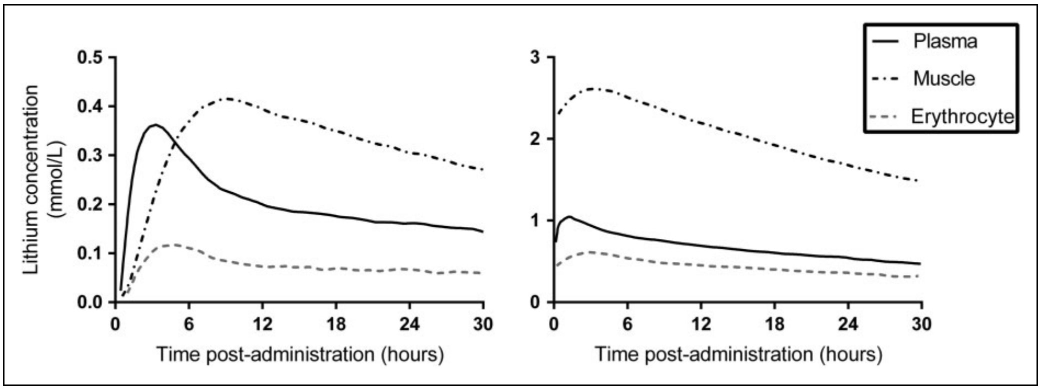

Figure 1. Multicompartmental kinetics of lithium and the effect of duration of therapy. Concentration–time profiles in patients following oral administration of lithium carbonate 600 mg. The graph on the left shows the profile in patients naive to lithium, and the graph on the right shows the profile in patients who had been taking lithium carbonate for 1 month. Plasma and erythrocyte lithium concentrations were measured, but muscle concentrations were estimated by pharmacokinetic modeling. Note that the y-axes differ between the graphs. Adapted from Ehrlich et al with permission.[36]

Box 2. Clinical Manifestations of Lithium Poisoning.

Organ system	Manifestation
Cardiovascular	Wandering atrial pacemaker,[73] sinus bradycardia,[74] ST-segment elevation,[73] unmasking Brugada syndrome,[75] prolonged QT interval Uncommonly, life-threatening arrhythmias[12]
Neurological	Lethargy, ataxia, confusion, agitation, neuromuscular excitability (irregular coarse tremors, fasciculations, myoclonic jerks, hyperreflexia) Severe lithium toxicity can manifests as seizures, including nonconvulsive status epilepticus
Gastrointestinal	Nausea, vomiting, diarrhoea, ileus

The most commonly used system for classification of severity of lithium toxicity is the one developed by Hansen and Amdisen in 1978[8] (see Box 3). This classification has considerable limitations as the patient population from which it was derived mostly consisted of patients with chronic toxicity, reducing its applicability in correlating lithium concentrations with toxicity in acute poisonings.[11]

Box 3. Relationship Between Severity of Chronic Lithium Toxicity and Plasma Concentrations.

Plasma Lithium Concentration[8,29] (mmol/L)*	Severity (Hansen and Amdisen Classification[8])
1.5-2.5	Grade 1 (mild) nausea, vomiting, tremor, hyperreflexia, agitation, ataxia, muscle weakness
2.5-3.5	Grade 2 (moderate) stupor, rigidity, hypertonia, hypotension
>3.5	Grade 3 (severe) coma, convulsions, myoclonia, collapse

*To be interpreted 12 hours after the last dose. Concentration range is indicative only, largely based on data from a small number of patients with largely chronic exposures. We believe that these concentrations have no role in assessment of patients with an acute ingestion, see text and Table 1

Persistent Manifestations

Previous studies have noted that a small proportion of patients with lithium poisoning and neurotoxicity have incomplete recovery.[8,16-18] These, and renal effects, are summarized in Box 4. Adityanjee et al[19] performed a literature review and identified 90 cases of neurological deficits following lithium poisoning that persisted for longer than 2 months. While some of the neurological findings may be unrelated to lithium poisoning, such as monocular papilledema,[20] the majority of the patients in this case series had persistent cerebellar dysfunction, including ataxia, dysarthria, and dysmetria. Investigations in patients with persisting cerebellar signs following lithium poisoning note irreversible cerebellar toxicity on computed tomography,[18] magnetic resonance imaging,[21] and histology,[22] including neuronal loss and gliosis of cerebellar gray matter. Cognitive impairment has also been reported and attributed to lithium poisoning[23]; however, this was in older patients taking coingestants that affect cognition such as benztropine and high-dose haloperidol. The influence of nutrient deficiencies, such as thiamine, was also not apparent from these data.

Box 4. Persistent Manifestations of Lithium Toxicity

Cerebellar: ataxia, dysarthria, dysphagia
Cognitive: impaired memory, attention, executive control, visuospatial deficits
Renal: Tubulointerstitial nephropathy, nephrogenic diabetes insipidus

Adityanjee suggested the term syndrome of lithium-effectuated neurotoxicity (SILENT)[24] to describe these findings; however, to date little is known about the syndrome as reported, including lithium and causation, epidemiology, or risk factors. Furthermore, there have been no long-term prospective cohort studies to ascertain prognostic information. Finally, the influence of administered treatments, such as enhanced elimination, on these outcomes is incompletely described in the literature.

Chronic lithium therapy is associated with an increased risk of acquired hypothyroidism, which has, in turn, been identified as an independent risk factor for developing neurotoxicity in patients with chronic poisoning.[9]

Risk Assessment

A comprehensive assessment can risk stratify individuals who present with lithium poisoning and help determine the most appropriate approach to management. Factors to consider include:

- The amount ingested and time course (acute, acute-on-chronic, or chronic),
- Presence of signs and symptoms (see Box 2),
- The formulation of the product (standard vs controlled release),
- Plasma lithium concentration,
- Patient factors,
- Availability of treatment modalities in the hospital or health-care setting

Two examples of acute lithium poisoning that differed in terms of formulation and history of lithium usage are shown in Figure 2. These cases will be used to exemplify various principles discussed here.

Amount Ingested and Time Course

Data regarding thresholds for the amount of lithium ingested that may prompt intervention are limited and relate to the context of the exposure. Instead, the time course of poisoning is probably a more important determinant of the risk of toxicity. This reflects the various factors that influence the relationship between plasma and brain lithium concentration–time profiles, in particular kidney function, as discussed above (see Section "Influence of the pattern of exposure on lithium pharmacokinetics, and the onset and offset of toxicity")

Acute poisoning. It is generally stated that ingestion of >7.5 mg/kg of elemental lithium (approximately 40 mg/kg of lithium carbonate) is associated with an increased risk of toxicity. This dose corresponds to a concentration of 1.4 mmol/L elemental lithium in the body water phase. However, acute overdoses generally confer a better prognosis due to the lower risk of neurotoxicity because lithium will not have had sufficient time to accumulate in the brain or other tissues, relative to the shorter time required for distribution to less toxic sites (eg, erythrocytes, muscle) and excretion (see Figure 1). Figure 2B shows a patient with acute poisoning who did not develop toxicity.

This phenomenon is supported by a number of recent case series. Based on the severity classification outlined in Box 4, a retrospective study reported that none of the 28 patients who presented with an acute overdose developed severe neurotoxicity.[9] Chen et al[25] reviewed a series of patients with acute ingestions of up to 9 g of lithium and found no patients developed severe toxicity. Gadallah et al[26] reported similar findings and a UK poisons information center noted that only 4.8% of patients with acute poisoning had moderate to severe toxicity.[10] A series from the California poison control system reported a higher prevalence of altered level of consciousness in acute poisonings (50%)[12]; however, few of these developed seizures or required intubation. The reasons for the difference in outcomes in the latter study is unclear but may relate to the categorization of altered level of consciousness which was not defined in the study. As such, marked CNS toxicity is less common in uncomplicated acute poisonings[9,11] despite high plasma concentrations.

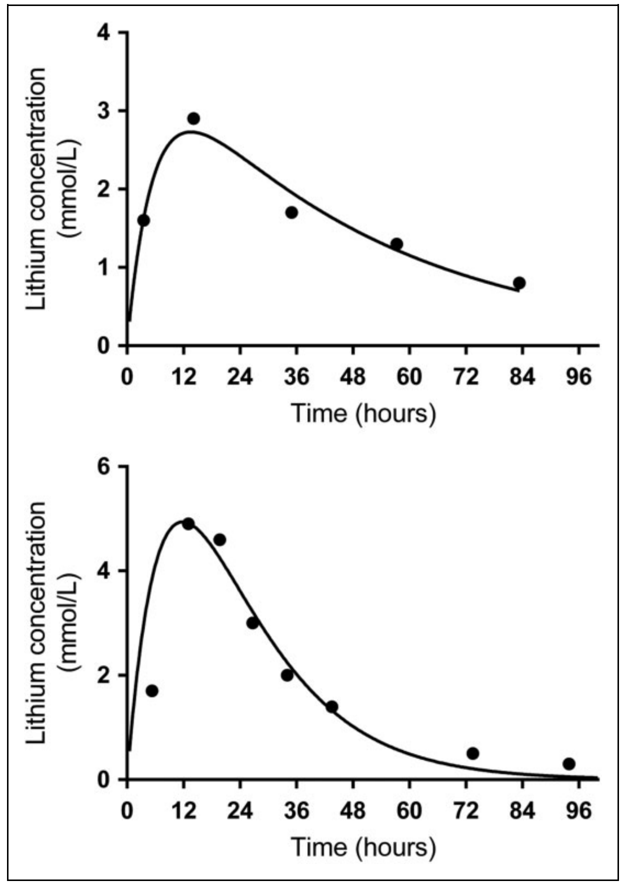

Figure 2. Concentration–time profiles in 2 patients with intentional self-poisoning with lithium. In both, the maximum concentration occurred at approximately 12 hours postingestion, but the apparent elimination half-life differed. A, 50 year-old woman taking chronic lithium (control unknown) with an acute overdose of 15 g of lithium carbonate (immediate release formulation). She had normal renal function throughout, treatment limited to intravenous fluids, and the apparent elimination half-life was 32 hours. She did not demonstrate lithium toxicity. B, A 35-year-old woman naive to lithium with an acute overdose of 13.5 g of lithium carbonate (sustained release formulation) with some coingestants. She had normal renal function throughout, was given whole bowel irrigation between 6 and 12 hours postingestion, administered intravenous fluids throughout, and the apparent elimination half-life was 10.5 hours. She did not demonstrate lithium toxixity.

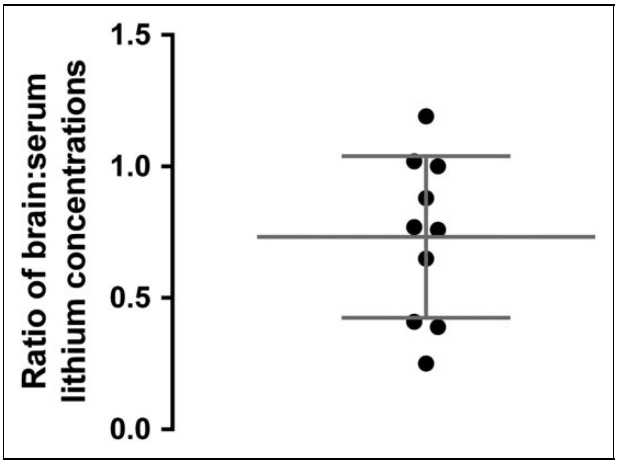

Figure 3. Interindividual variability in brain to serum lithium concentrations. Data obtained in 10 patients after 4 to 8 weeks of chronic lithium at a fixed dose (mean 0.7, standard deviation 0.3).[76] Mean dose was 855 ± 142 mg lithium carbonate. Brain lithium concentrations were measured using magnetic resonance spectroscopy.

Acute-on-chronic poisoning. Here, the risk of neurotoxicity is higher than in acute poisoning because some lithium has already distributed to the intracellular space in the CNS prior to poisoning.

A series of cases referred to a UK poisons information center noted that 20% (5 of 25) with acute-on-chronic lithium poisoning (and no other coingestants) had moderate-severe toxicity.[10] Further, a series of cases referred to a US PCC noted that 48% of cases had an altered level of consciousness, 4% required intubation, and that seizures were reported in 0.8% of cases.[12]

As the CNS compartment already contains lithium, a smaller amount of lithium is required to distribute to that space to cause neurotoxicity compared to acute poisoning. Plasma lithium concentrations do not necessarily correlate with toxicity, as in acute poisoning, because a steady-state concentration will not be achieved with the intracellular space (Figure 1). For example, a case report[27] noted an asymptomatic patient who did not receive dialysis despite very high plasma lithium concentrations (10.6 mmol/L at 13 hours after ingestion) with acute-on-chronic poisoning. Figure 2A shows a case of acute-on-chronic poisoning in which toxicity did not develop despite a high lithium concentration.

Chronic poisoning. This mode of poisoning confers the highest risk of neurotoxicity for 2 reasons.[9] First, the time course (usually weeks) maximizes the opportunity for lithium to distribute to the CNS compartment and to accumulate in neural tissue and induce toxicity.[15,28] As steady state has been achieved in this circumstance, plasma lithium concentrations correlate better with CNS concentrations at the time of presentation and patients may exhibit intoxication at concentrations close to the therapeutic range (Figure 1). However, even at steady-state conditions, there is marked interindividual variation in the ratio of brain to serum lithium concentrations (Figure 3). Further, delayed presentations relative to the last dose, for example, in patients too confused to take their medications, can cause the lithium concentration to be low despite persistence of clinical toxicity.

Second, the half-life of lithium is prolonged in chronic poisoning compared to acute[29] which reflects both the redistribution of lithium from the intracellular compartment to the vascular compartment and possibly changes in renal handling of lithium such as seen in nephrogenic diabetes insipidus. This principle is demonstrated in Figure 2, where the apparent elimination half-life in Figure 2A, which was a patient on chronic therapy, exceeds that of Figure 2B in which the patient was naive to lithium therapy.

Chronic poisoning can be secondary to prescribing, dispensing or dosing errors, or other factors that increase lithium exposure as mentioned previously. Common causes include volume depletion from dehydration, nephrogenic diabetes insipidus or intercurrent illness, hypothyroidism, or drug interactions.

In the Australian case series mentioned previously, 94% of the cases of severe poisoning occurred in patients with chronic poisoning[9] and moderate to severe poisoning was noted in 24% of patients with chronic poisoning in the UK study.[10] In the series of cases referred to US PCC, 81% of cases had an altered level of consciousness, 5% required intubation, and 3.2% of cases reported seizures.[12]

Signs and Symptoms of Lithium Intoxication

Lithium exerts its primary toxicity in the CNS (the toxic compartment,[14] Boxes 1 and 3) which necessitates a comprehensive neurological assessment in each patient for evidence of neurotoxicity. Because neurotoxicity reflects the concentration of lithium in the brain, and because the time taken for distribution to the CNS occurs over hours (see Section "Influence of the pattern of exposure on lithium pharmacokinetics, and the onset and offset of toxicity", and Figure 1), serial clinical assessments are required. However, a single study noted that patients who developed severe symptoms from chronic poisoning were symptomatic at the time of presentation.[9]

As always, it is necessary to interpret clinical findings in light of differential diagnoses. For example, coingestion of other xenobiotics can confound clinical assessment, notably serotonergic agents that also manifest with tremor and/or hyperreflexia or sedative medications and ethanol which can falsely lower the level of consciousness.

Formulation

Lithium is available either as an immediate or as a controlled-release formulation. Box 5 summarizes the differences in pharmacokinetic properties based on formulation and dose, which are relevant for the interpretation of plasma lithium concentrations and may influence decisions regarding gastrointestinal decontamination.

Box 5. Pharmacokinetics of Lithium Formulations.[a]

Pharmacokinetic Parameter	Immediate Release	Controlled Release
Bioavailability	95%-100%	60%-90%
Tmax with therapeutic dosing (hours)	1-6 (may be delayed in overdose)	4-12
Change in kinetics in overdose	Delayed Tmax	Delayed second peak reported in overdose[30]

[a]Tmax = time to maximum concentration.

Controlled-release preparations are associated with greater risk of neurotoxicity due to the potential for multiple delayed peak concentrations.[30] They can also form pharmacobezoars (concretions of aggregated tablets) which can lead to prolonged and erratic absorption, and in some rare cases prompt removal by endoscopy.[31] The cause of pharmacobezoar formation is unclear but may include the ingested dose exceeding drug solubility or the properties of the drug delivery system.

Figure 2B demonstrates that a complicated concentration–time profile may not necessarily occur, relative to that observed for immediate release formulations. In this case, this observation may relate to the amount ingested or the decontamination administered.

Plasma Lithium Concentrations

Lithium has a narrow therapeutic index, whereby the target plasma concentration during initiation (eg, acute mania) is 0.6 to 1.2 mmol/L, and for prophylaxis in chronic therapy is maintained between 0.4 and 1.0 mmol/L. Lithium concentrations have been measured with the purpose of confirming an exposure and estimating body burden, but there is debate regarding their usefulness for predicting the development of toxicity. There have also been reports of patients developing signs of lithium toxicity with apparently therapeutic lithium concentrations.[32,33]

Lithium concentrations need to be interpreted with consideration of the time since ingestion (the above reference range is based on a trough concentration at least 12 hours post-ingestion) and pattern of exposure, given the pharmacokinetic principles outlined above and demonstrated in Figure 1. This is necessary for relating the initial plasma lithium concentration to the likely concentration in the CNS. A shortcoming of the existing literature is that these data are incompletely reported.[34]

A relationship between plasma lithium concentrations and severity has been reported[8,29] (see Box 3). It is emphasized that these concentration ranges are based on steady-state lithium plasma concentrations *at least 12 hours post-ingestion*. Plasma lithium concentrations lower than those listed here have been reported to be associated with severe toxicity in other series which relates, in part, to interindividual variability in the ratio of brain to serum lithium concentrations (Figure 3). Waring et al[10] noted that the incidence of severe toxicity was higher in the chronic poisoning group compared with acute poisoning despite similar median plasma lithium concentrations (2.4 mmol/L compared to 2.3 mmol/L, respectively). Oakley et al[9] reported that patients with severe toxicity, which were largely chronic poisoning, had higher plasma lithium concentrations than those without severe neurotoxicity (2.3 compared to 1.6 mmol/L).[9,10] In acute overdose, lithium concentration should not be assumed to be at steady state; therefore, plasma concentrations must be analyzed in view of the history and physical exam, the delay since ingestion, the pre-overdose lithium body load, and an evaluation of the kidney function, preferably in a serial manner rather than an interpretation based on a single lithium measurement.

In acute overdoses, there is poor correlation between random plasma lithium concentrations and toxicity. There are many reports of patients with acute overdoses and lithium concentrations much higher than 3.5 mmol/L who have made full recovery without developing toxicity or requiring ECTR.[13] Both cases shown in Figure 2 did not develop toxicity despite lithium plasma concentrations at 12 hours that would predict toxicity in Box 3. This lack of relationship can be explained by the discordance between lithium concentrations in plasma and other tissues (Figure 1), including the brain[28] which is the main site of toxicity (see Section "Influence of the pattern of exposure on lithium pharmacokinetics, and the onset and offset of toxicity"). As noted above and in Box 3, the stated ranges of plasma lithium concentrations were based on data obtained 12 hours after the last dose.

Therefore, as stated previously, given the wide range of factors influencing temporal changes in lithium concentrations in the plasma and brain, attempts to predict the risk of toxicity based on plasma lithium concentrations in isolation (without such information) are complicated and error prone.

Whole Blood or Red Blood Cell Lithium Concentrations

It has been proposed that measurement of the concentration of lithium in whole blood, or erythrocytes, may provide a useful estimate of intracellular concentration elsewhere in the body, such as the brain. However, this does not appear to be useful in risk assessment or management decisions,[35] which may reflect the differing extent that lithium accumulates in tissues in the body (Figure 1). For example, the plasma–muscle concentration ratio usually exceeded 2, while the plasma–erythrocyte concentration ratio was usually less than 0.5 (and these authors hypothesize that muscle is more similar to brain than the erythrocytes).[35] This appears to be a result of differences in the ratio of the rates of distribution (determined using rate constants, k) into and out from erythrocytes and muscle in patients taking lithium.[36] Specifically, the mean ratio of influx–efflux for erythrocytes was 0.32 in patients naive to lithium and 0.55 in patients already taking lithium; in contrast, for muscle the ratios were 1.8 and 4.2, respectively.[36] However, it should be remembered in both cases that net lithium movement also reflects the concentration in each compartment; as such, net efflux is maximized when the plasma concentration is very low. This has implications for treatment.

To add further complexity to these pharmacokinetic observations, data in rats note that the rate and extent to which lithium is taken up in the brain vary between different brain regions.[37]

These data underscore the importance of interpreting lithium plasma concentrations in the context of the exposure. Despite the complexities and limitations, several guidelines list recommendations for instituting and stopping ECTR on the basis of lithium plasma concentrations (Table 1), which will be discussed in detail in the next section.

Patient Factors

A retrospective study[9] found that 3 patient factors were independently associated with severe neurotoxicity due to lithium. These were nephrogenic diabetes insipidus (adjusted odds ratio [OR] 26.96, 95% confidence interval [CI] 2.89-251.94), age older than 50 years (adjusted OR 6.2, 95% CI 1.36-28.32) and thyroid dysfunction (adjusted OR 9.30, 95% CI 1.36-63.66). There was a trend in baseline renal impairment (adjusted OR 6.49, 95% CI 0.98-43.01), and hyperparathyroidism was also noted in 3 cases of severe neurotoxicity, but these did not reach statistical significance. Although statistically significant, the CIs were wide due to the size of the study. There is rationale supporting each risk factor, as discussed below, but more data are required to confirm the strength of the association.

Nephrogenic diabetes insipidus: the most common renal side effect of lithium,[38] which predisposes the individual to volume depletion, in particular free water, with consequent activation of the renin–angiotensin aldosterone system which promotes lithium reabsorption.

Age older than 50 years: It may reflect age-related reduction in physical reserve and/or increased prevalence of polypharmacy associated with this age-group that predisposes to lithium poisoning. Corcoran et al[39] observed that individuals with intoxication had advanced cerebral arteriosclerosis, suggesting that organic brain disease predisposes the individual to neurotoxicity.

Renal impairment: Lithium excretion is almost exclusively dependent on glomerular filtration rate (GFR), so it is unsurprising that renal impairment predisposes the patient to development of severe neurotoxicity unless accompanied by an appropriate dose reduction. A guide to what degree of renal impairment is important when considering initiation of an ECTR is[13]:

- Estimated GFR < 45 mL/min/1.73 m^2
- Kidney Disease: Improving Global Outcomes stages 2 or 3 acute kidney injury
- In adults without a baseline serum creatinine, serum creatinine > 176 μmol/L in adults, or > 132 μmol/L in the elderly patients or those with low muscle mass
- Serum creatinine greater than 2 times the upper limit of normal for age and weight in children without a baseline serum creatinine concentration
- The presence of oligo/anuria

Thyroid dysfunction: The prevalence of clinical hypothyroidism is increased in patients taking lithium therapy (OR 5.78, 95% CI 2.00-16.67)[38] which can cause a reduction in GFR.[40] Conversely hyperthyroidism can increase lithium reabsorption thereby reducing lithium excretion.[41] Hypothyroidism is associated with the development of severe neurotoxicity from lithium with an adjusted OR of 9.30 (95% CI 1.36-63.66).[9]

Hyperparathyroidism: This is a known complication of lithium therapy[38] and may lead to volume depletion secondary to the osmotic effects of hypercalcemia.

Management of Lithium Toxicity

General Principles

The general approach to any poisoned patient involves assessment and stabilization of the airway, breathing and circulation in an appropriately monitored environment. While the CNS is the primary organ of toxicity, there are reports of cardiac (including death[12]) and renal toxicity and these organ systems must also be appropriately monitored. Assessment of renal function is important for guiding treatment, including intravenous fluids and consideration of enhanced elimination using an ECTR. Medications that promote lithium toxicity (Box 1) should be ceased, if possible.

Fluid resuscitation will optimize renal perfusion thereby maximizing lithium excretion, and the use of normal saline (0.9% NaCl) has a theoretical benefit of reducing lithium tubular reabsorption by providing an additional sodium load.[42] Regular clinical assessments of fluid balance are necessary to ensure that patients are adequately rehydrated and maximal renal elimination is obtained.

Per local protocols, other routine investigations for acute poisoning should be considered, including an electrocardiogram, acetaminophen (paracetamol), and salicylate concentrations on admission, and beta-human chorionic gonadotropin level in women of childbearing age.

In addition to supportive care including intravenous fluids, airway management, and gastrointestinal decontamination for acute ingestions, the key interventions for lithium toxicity are ECTR, in particular hemodialysis, hemofiltration, or a hybrid ECTR. Decisions for the use of these treatments are based on symptoms and signs, or lithium concentrations (while acknowledging complexity in their interpretation), which vary depending on the context of the exposure and the patient. These are summarized in Table 1.

Due to the likelihood for dynamic changes in plasma lithium concentrations post-admission, whether relating to ongoing absorption or endogenous distribution and elimination (see Figures 1 and 2), serial lithium plasma concentrations are

Table 1. Indications for Specific Treatments in Patients With or at Risk of Lithium Toxicity.

Indication	Emedicine (United States) (http://emedicine.medscape.com/. Accessed January 12, 2016)	EXTRIP Workgroup Recommendations[13,a]	Goldfrank's *Toxicologic Emergencies*, 10th Ed.[76,a]	*Olson's Poisoning and Drug Overdose*, 6th Ed.[77]	Toxbase (United Kingdom) (http://www.toxbase.org/. Accessed January 12, 2016)	*Toxicology Handbook*, 3rd Ed.[78]	Toxinz (New Zealand) (http://www.toxinz.com/. Accessed January 12, 2016)	UpToDate (United States) (http://www.uptodate.com. Accessed January 12, 2016)	Wikitox (http://curriculum.toxicology.wikispaces.net/2.1.11.9.4+Mood+stabilizers. Accessed January 12, 2016)
Decontamination with whole-bowel irrigation									
Exposure	Controlled-release tablets		Controlled-release tablets	Controlled-release tablets	Controlled-release tablets			>10 controlled-release tablets	50 g immediate release
Symptoms			Neurological dysfunction						
Time since ingestion (hours)								Within 2-4 hours	Within 1-2 hours
Comments	Specific recommendation not provided	Not mentioned	Both of the above. Ensure protected airway and no obstruction or ileus	Specific recommendation not provided	>4 g by adults or definite ingestion of a substantial amount by a child	Not recommended	Contraindicated	Both of the above	Not usually required in acute overdose if normal renal function and sodium replete
Enhanced elimination using sodium polystyrene sulfonate									
Comments	Mentioned, but specific indications not provided	Not mentioned	Not recommended	Not recommended	Not mentioned	Not mentioned	Not mentioned	Not recommended	Not mentioned
Enhanced elimination using an extracorporeal treatment									
$[Li^+]$ in acute scenario	≥4 mmol/L	>5 mmol/L (suggested)	>6 mmol/L		>5 mmol/L			>4 mmol/L	
$[Li^+]$ in chronic exposure	≥2.5 mmol/L		>5 mmol/L		>2.5 mmol/L	>2.5 mmol/L with neurological dysfunction	> 4 mmol/L	>2.5 mmol/L	>2.5 mmol/L
Symptoms	Decreased consciousness, seizures, or life-threatening dysrhythmias	Confusion (suggested), neurological features or dysrhythmias	Acute neurological dysfunction (confusion, decreased consciousness, seizures); hyperthermia (suggested). Severe signs and symptoms of neurotoxicity	Seizures or severely abnormal mental status	Neurological features such as decreased consciousness, cerebellar signs, or convulsions	Neurotoxicity	Neurological signs and symptoms	Significant toxicity and > 2.5 mmol/L	Seizures, coma, hypotension not responsive to fluids
Renal failure[b]	>4 mmol/L	>4 mmol/L	>3 mmol/L	Yes		Particularly those with clinical features of neurotoxicity	Neurological signs and symptoms	>2.5 mmol/L	CrCL <60 mL/min

(continued)

Table 1. (continued)

Indication	Emedicine (United States) (http://emedicine.medscape.com/. Accessed January 12, 2016)	EXTRIP Workgroup Recommendations[13,a]	Goldfrank's *Toxicologic Emergencies*, 10th Ed.[76,a]	*Olson's Poisoning and Drug Overdose*, 6th Ed.[77]	Toxbase (United Kingdom) (http://www.toxbase.org/. Accessed January 12, 2016)	*Toxicology Handbook*, 3rd Ed.[78]	Toxinz (New Zealand) (http://www.toxinz.com/. Accessed January 12, 2016)	UpToDate (United States) (http://www.uptodate.com. Accessed January 12, 2016)	Wikitox (http://curriculum.toxicology.wikispaces.net/2.1.11.9.4+Mood+stabilizers. Accessed January 12, 2016)
Other	Patients unable to tolerate saline (eg, CCF or liver disease). Guidelines based on levels alone are controversial	If the expected time to obtain a $[Li^+]$ < 1 mmol/L with optimal management is >36 hours (suggested)	Minimal signs of toxicity but unable to tolerate saline repletion (eg, CCF, sepsis)	There is no consensus on which level is an indication for ECTR	$[Li^+]$ > 4 mmol/L in acute on chronic exposures. Risk of rebound when dialysis is stopped. Clinical improvement generally takes longer than reduction of plasma lithium concentrations. Prolonged or repeated treatments may be required.	IHD is first-line modality; prolonged and repeated treatments may be required	Repeat IHD if > 1 mmol/L 6-8 hours post-IHD. Patients unable to tolerate volume expansion	>2.5 mmol/L in patients unable to tolerate volume expansion	

Abbreviations: CCF, congestive cardiac failure; CrCL, creatinine clearance; ECTRs, extracorporeal treatments; IHD, intermittent hemodialysis.
[a] What was "recommended" unless otherwise stated.
[b] Variably defined, see text, for examples, of impaired kidney function.

required in patients with no or minimal symptoms. We recommend concentrations approximately every 4 hours initially, depending on how recently lithium was ingested or when intravenous fluids were commenced. For example, following a recent large ingestion, it may be useful to measure concentrations more frequently (eg, every 2-3 hours on 3 occasions) to gain an appreciation of the rate of change in guide decisions regarding decontamination or transfer for ECTR. If a slower rate of increase, the frequency can be dropped to every 4 to 6 hours. The peak lithium concentration may not be apparent until 12 to 24 hours post-ingestion depending on the formulation, amount, and patient details, as noted in Figure 2. Following this, the frequency can be dropped even further, for example, every 6 to 12 hours depending on the clinical situation.

Blood samples can be obtained less frequently if the patient remains asymptomatic or if there is a consistent and significant decrease in lithium concentrations.

In patients with an elevated creatinine plasma concentration on admission, it is also useful to monitor how this changes in response to initial treatment because this will influence decisions regarding escalation to an ECTR.

For obvious reasons, sample collection in a tube containing lithium heparin should be avoided and if a sharp increase in the lithium concentration is noted then the sample should be repeated to confirm that it is not due to a sampling error.

Decontamination: Whole-Bowel Irrigation

Whole-bowel irrigation (WBI) with polyethylene glycol solution can reduce the absorption of lithium in patients with large acute ingestions, particularly of sustained-release preparations of lithium.[43] A retrospective observational study showed that patients who underwent WBI (but many also received sodium polystyrene sulfonate [SPS]) had lower poisoning severity scores, lower peak plasma lithium concentration and higher Glasgow Coma Scale (GCS) scores.[44] As shown in Figure 2, with WBI the absorption phase did not appear to differ based on formulation.

A recent position paper stated that WBI can be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs not otherwise adsorbed by activated charcoal such as lithium,[45] but specific indications were not provided. Recommended indications for WBI are summarized in Table 1, and our practice is to consider its use when there is an acute ingestion of a significant amount (at least 80 mg/kg lithium carbonate but often much more) of a sustained-release formulation. The usual WBI regimen in adults is 1 to 2 L/h of polyethylene glycol, via a nasogastric tube until the rectal effluent is clear. Clinicians need to make the decision to perform endotracheal intubation to protect the airway for the purpose of WBI, taking into account the current and expected change in mental status of the poisoned patient.

Enhanced Elimination

Individuals with severe lithium toxicity require enhanced elimination to reduce the duration of admission and potentially minimize the risk of neurotoxicity. A number of modalities can reduce plasma lithium concentrations; however, in the absence of randomized controlled trials, the evidence for each is low.[13,46]

Indications for enhanced elimination vary depending on the resource consulted (see Table 1), but most consider that the presence of clinical signs of neurotoxicity are a strong indication. Each modality will be discussed separately, with a focus on extracorporeal removal, which is the most common method used.

Sodium Polystyrene Sulfonate

Sodium polystyrene sulfonate is an ion exchange resin that can be used as an adjunctive treatment for the management of hyperkalemia. Linakis et al[47] demonstrated that SPS was effective at decreasing lithium absorption in animals, and a small pharmacokinetic study demonstrated that SPS increases clearance of lithium in healthy volunteers.[48] A retrospective study showed that addition of SPS to best supportive care resulted in a lower peak lithium concentration[49]; however, it was a small study of chronic poisonings only and no clinical end points were included in the analysis. The role of SPS is reduced by its limited capacity to bind lithium, necessitating large volumes of SPS to achieve a useful clearance. Use of SPS confers a risk of precipitating hypokalemia, so many sources do not currently advise its use in lithium toxicity (Table 1). Its role in the routine management is yet undefined and probably limited, but it may be considered adjunctive therapy in patients with chronic lithium poisoning that are not otherwise amenable to an ECTR due to geographical constraints or other patient-related factors.

Extracorporeal Treatments

Lithium has several physical properties that make it an easily dialyzable xenobiotic, including that it is small (6.94 Da), unbound to plasma proteins, and has a relatively small volume of distribution (0.8-1.2 L/kg) and relatively slow endogenous clearance (15-20 mL/min).

A rapid reduction in plasma lithium by dialysis may either prevent accumulation in the brain (toxic compartment) and/or establish a favorable concentration gradient, facilitating the diffusion of lithium back into the plasma (nontoxic compartment). This forms the theoretical basis for how ECTR can reduce the risk of neurotoxicity or promote recovery; however, at present the evidence to support this practice is limited to case studies and series and expert consensus.[13,46]

The basis for many current guidelines arise from recommendations from the seminal paper published by Hansen and Amdisen which suggested that dialysis be instituted in patients who have plasma lithium concentrations above 2.5 mmol/L that cannot be reduced to 1 mmol/L within 30 hours based on serial measurements.[8] However, this study and other studies may be biased in favor of ECTR, which has not been fully addressed in subsequent studies. A case series found that outcomes were similar in patients who received ECTR compared to those who did not undergo ECTR despite it being recommended by a PCC.[11] A lack of patient-level information prevented further analysis into the reason for the nonadherence to the advice of the PCC, but these data may prompt questions regarding the benefit of ECTR in unselected cases, particularly in the absence of severe toxicity.

Further, ECTR can confer risks relating to the treatment. There are reports of a paradoxical deterioration in consciousness with rapid reductions in plasma lithium concentrations,[50] which may reflect rapid osmotic shifts with chronic poisoning. There is also a risk of vascular injury, including arterial puncture (although less of an issue with modern use of ultrasound-guided techniques) and catheter-related sepsis and thrombosis, which are also less of a concern, given the short-term requirement for this procedure for poisoning cases than for other indications of ECTR.

Indications for ECTR. There is significant variability in clinical decision-making when it comes to using ECTR in the management of lithium poisoning[51] and this is reflected in similar variability among current resources in regard to thresholds for instituting various treatments (Table 1). The reason for the lack of consensus possibly relates to the absence of randomized controlled trial data and the heterogeneous nature of the population who present with lithium intoxication.

The other confounding difficulty is the discordance between random plasma lithium concentrations and toxicity observed in acute overdoses, yet these concentrations are often relied upon too heavily as a primary guide to management. Patients with high plasma lithium concentrations in the early stage of an acute intoxication are often asymptomatic except for gastrointestinal signs (eg, see cases in Figure 2), but are theoretically at risk of subsequent toxicity, depending on the rate of excretion.

As such there *may be a potential* benefit to instituting preemptive ECTR even if the patient is asymptomatic but with a lithium concentration that is predicted to remain in the toxic range for a protracted period of time. Hansen and Amdisen[8] recommended ECTR in patients with chronic poisoning and plasma lithium concentrations greater than 2.5 mmol/L, and if it would take greater than 30 hours for the concentration to drop below 1 mmol/L. More recently, an expert consensus process suggested ECTR if lithium plasma concentration was not <1 mmol/L within 36 hours.[13]

These recommendations indicate that it is not necessary to initiate ECTR immediately in all cases, particularly if the patient is asymptomatic. Instead, the rate of change following the institution of treatment can be monitored for a few hours in the first instance. However, in most cases, these recommendations appear to be based on expert consensus and the importance of the specific indications is not confirmed. The concentration–time profile for both patients in Figure 2 would be indications for ECTR with regard rate of elimination criteria, yet neither received ECTR nor developed toxicity. More research is required in this area.

What is apparent from this discussion is that if the excretion of lithium is reduced in a patient, whether due to impaired renal function (see above) or other risk factors (Box 1), the risk of developing toxicity increases.

Choice of modality. Intermittent hemodialysis (IHD) is the usual recommended extracorporeal modality for treatment of lithium intoxication, but the use of continuous renal replacement therapy (CRRT; a lower efficiency ECTR utilizing hemodialysis and/or hemofiltration) is an acceptable alternative where IHD is not available or cannot be undertaken due to clinical instability (although fluid removal is seldom required in lithium intoxication, so ECTR-associated hypotension is uncommon).[13]

Lithium clearance during high-efficiency IHD can be as high as 170 mL/min, which is markedly higher than endogenous renal clearances, which averages approximately 20 mL/min.[52] Although, case series of patients with lithium poisoning note endogenous clearance to be approximately 10 mL/min due to impaired kidney function.[13] Clearance from ECTR and endogenous renal function are independent and additive to each other. However, it is important to recognize that lithium clearance from tissue compartments is much slower than from the plasma compartment and may be as low as 10 mL/min.[53] This has implications for removal of lithium from the toxic compartment (brain), where changes in the intracellular lithium concentration lag behind those of the plasma concentration.

A rebound in lithium plasma concentration after IHD is completed occurs when the rate of elimination of lithium from plasma by ECTR exceeds the rate of lithium redistribution from the extravascular compartments back to the blood (central compartment) or when ongoing absorption is occurring. It is most likely to occur to a significant degree following high-efficiency treatments such as IHD.[54] A rebound in lithium concentrations may prompt retreatment with an ECTR in the interests of facilitating recovery, but few patients (if any) exhibit clinical deterioration due to the rebound. It was reported that rebound may actually represent shifts from brain to blood.[8,13]

Recommendations by the Extracorporeal Treatment in Poisoning Group (EXTRIP) include that after an initial treatment with IHD, the use of CRRT or further cycles of IHD are equally acceptable.[13] Although there is no head-to-head comparison of these 2 methods, evidence from simulation models suggests that initial treatment with IHD followed by CRRT results in better clearance of the intracellular compartment than either sole CRRT or a single therapy with IHD.[55]

There is insufficient experience with newer ECTR modalities to recommend their use first-line in the treatment of lithium intoxication at this time, but early data are positive. For example, case reports note that sustained low-efficiency dialysis (SLED) lowers the lithium plasma concentration,[56] that it may be more efficient at improving lithium clearance than CRRT and of similar efficiency to IHD.[57] More data on lithium clearance by newer ECTR modalities are of interest, and recent guidelines clarify the minimum data set required to achieve this.[58]

CRRT is associated with a reduced likelihood of rebound in plasma lithium concentrations but at the cost of a lower clearance compared with IHD.[54] A mean clearance of 43.1 (range

19-64) mL/min is achieved, depending on the type of regimen prescribed.[13] Generally, it is recommended that CRRT requires 24 hours of continuous therapy to decrease lithium to a similar extent as that achieved from 4 hours of IHD, due to the slower clearance.

Peritoneal dialysis is relatively inefficient for removal of lithium in the poisoned patient with mean lithium clearance of only 10.9 (range 9-14) mL/min, which is similar to that achieved by endogenous clearance.[13,59] The combination of low-efficiency toxin removal, technical difficulties of Tenckhoff catheter insertion in the acute setting, and requirement of long dialysis sessions and frequent exchanges makes peritoneal dialysis a less favorable option for most patients. There is also no role for charcoal hemoperfusion in the treatment of lithium intoxication as lithium is not adsorbed to charcoal molecules and thus there is no enhancement of elimination.[60,61]

Technical aspects of ECTR. Each of blood and dialysate/filtration flows influence solute clearance by ECTR, where the slowest of these flow rates is the rate-limiting step for solute removal. In general, blood flow is lower than dialysate flow in IHD and the opposite is true with CRRT. Indeed, lithium clearance is almost proportional to blood flow during IHD and thus higher blood flows through the IHD filter can result in significantly higher lithium clearance from the plasma compartment.[59,62,63] With CRRT, a linear correlation exists between lithium clearance and the flow rate of the dialysate/filtrate.[63-65]

This means that clearance can be maximized by increasing blood flow during IHD and increasing dialysate/filtration flow during CRRT.[63] Countercurrent flow increases clearances of small molecules by 20% to 30%[66] and this should be preferred over concurrent flow where possible. Use of large filters also maximizes clearance.

When to stop ECTR. The decision about when to stop ECTR in the patient with lithium intoxication needs to take into account the risk of rebound in plasma lithium concentrations, which is not clearly defined. Where plasma lithium concentrations can be regularly monitored, ECTR can be stopped when the lithium concentration falls below 1 mmol/L and a clinical improvement is noted, as serious adverse outcomes are unlikely to occur at this concentration.[13]

Where lithium concentrations are not able to be readily monitored, ECTR should be performed for a minimum of 6 hours.[13] In the case of lower efficiency ECTRs such as CRRT, treatment should continue for at least 3 times the duration of IHD, for example, at least 18 hours, to achieve an approximately similar net clearance.

Given the potential for rebound in lithium plasma concentrations, it is important to regularly check lithium concentrations after completion of ECTR to ascertain the extent to which lithium concentrations rebound and requirement for further ECTR. Serial lithium plasma concentrations should be measured at regular intervals, for example, 2, 6, and 12 hours after the cessation of ECTR. If there is an early and significant rebound in plasma concentrations, then this may indicate ongoing absorption from a sustained-release formulation so further WBI should be considered. Otherwise, a later or slower rebound in lithium plasma concentration may reflect redistribution from extravascular sites and may call for reinitiation of ECTR. It may be required to extend monitoring of plasma concentrations for up to 72 hours after cessation if there is ongoing absorption suspected, for example, from sustained-release formulations where gastrointestinal decontamination was not adequately performed. Some studies have found that 2 IHD sessions are generally required to treat most cases of significant lithium intoxication.[59]

Diuretics

The addition of amiloride and/or furosemide may theoretically enhance lithium elimination by blocking reabsorption in the renal tubules. Also, amiloride is a proposed treatment for lithium-induced nephrogenic diabetes insipidus. Amiloride blocks the epithelial sodium channel located at the apical membrane of the principal cells in the distal convoluted tubules and collection system, which may reduce reabsorption. However, a study in dogs found that the addition of amiloride resulted in only a 5% increase in fractional lithium excretion[67] and to an even lesser extent in salt-deplete humans.[68] Therefore, amiloride therapy is not likely to significantly enhance the elimination of lithium.

Furosemide inhibits lithium reabsorption by dissipating electronegative potential by inhibiting chloride absorption in the renal medulla,[69] with a resultant increase in lithium excretion.[70]

Despite the theoretical benefits, there has been little evidence from case series that the addition of either diuretic has beneficial effects on lithium pharmacokinetics,[52] and given that diuretics (in particular loop diuretics) are well-recognized risk factors of lithium toxicity (Box 1), their use in the treatment of lithium toxicity is not recommended.

Restarting Lithium

For patients in whom lithium has maintained good control of their mood disorder, there may be interest in restarting lithium after an overdose once there has been a clinical improvement and the lithium is at a therapeutic plasma concentration. This decision requires a multidisciplinary discussion with careful consideration of the likelihood of the patient becoming poisoned again, including risk of self-harm, a careful approach to monitoring and dose titration, above-mentioned comorbidities and outcomes (including health care utilization) in the event of repoisoning. This may include a review of the target plasma lithium concentration, depending on the circumstances of the admission, and considering the patient's diagnosis, demographics, and comorbidities.

The concomitant use of medications that may have contributed to the development of lithium toxicity should be reviewed. A number of potential drug interactions have been associated with hospitalizations for lithium poisoning, largely because they increase lithium plasma concentrations (see Box 1). A large single-center retrospective study[71] quantified the relative risk associated with recent commencement of angiotensin-converting enzyme inhibitors and loop diuretics as 7.6 and 5.5, respectively. Interestingly, the same study did not demonstrate an increased risk associated with the commencement of nonsteroidal anti-inflammatory medications or thiazide diuretics, which may have reflected appropriate dose adjustment due to clinician awareness regarding these interactions.

Additional pharmacodynamic drug interactions have been reported with the use of calcium channel antagonists[5,72] and neuroleptics[6]; however, the risk has not been quantified.

Conclusion

Although lithium is a valuable treatment option in mental health, careful attention to prescribing and monitoring of patients is required to reduce adverse outcomes. The toxicity of lithium is well described, as is the importance of the patterns of exposure on the risk of toxicity. Despite the establishment of expert consensus recommendations, more controlled data are needed. Current controversy include the specific criteria for intervention, the urgency of intervention, and what type of treatment is required. For example, data describing the benefits, if any, of preemptive enhanced elimination in an asymptomatic patient with very high plasma lithium concentrations are extremely limited. In patients with established lithium toxicity, although IHD appears effective at reducing the plasma lithium concentration, its influence on the time to resolution or the prevention of irreversible neurotoxicity is poorly defined. Other treatments that enhance elimination may have an equal effect or may even be preferred in some circumstances. Finally, the influence of patient comorbidities such as the degree of impaired kidney function is important and potentially overlooked. With such a wide range of factors contributing to clinical outcomes following lithium poisoning, and complexity with conducting adequately powered randomized controlled trials (low frequency of geographically disparate and heterogeneous exposures), case reports and series will continue to provide useful information for comparison against predictions made using more advanced computer-based pharmacokinetic modeling.

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