Management of lithium intoxication

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First received 18 Oct 2021
Final revision 30 Jan 2022
Accepted 1 Feb 2022

SUMMARY

Lithium is a gold standard maintenance treatment in bipolar affective disorder. It has a narrow therapeutic range, and at higher serum lithium levels there is a risk of adverse effects and toxicity. There are three patterns of lithium intoxication: acute, acute-on-chronic and chronic. We describe risk factors for lithium intoxication, mechanisms of toxicity and clinical symptoms seen in lithium intoxication. We describe both the acute and chronic effects of lithium toxicity. Lithium intoxication may be life-threatening and associated with longer-term sequelae. The management of lithium intoxication involves determining the type of intoxication. We discuss treatment strategies aimed at reducing absorption and increasing elimination of lithium. We discuss clinical indications for extracorporeal methods such as dialysis, which are used to limit the time and degree of exposure of the central nervous system to toxic lithium concentrations. Haemodialysis is the most rapid method of eliminating lithium from the body, but careful monitoring is required. Preventive strategies to mitigate the risk for lithium intoxication are discussed.

LEARNING OBJECTIVES

After reading this article you will be able to:
- describe the clinical characteristics of lithium intoxication
- outline risk factors for lithium intoxication
- understand the assessment and management of lithium intoxication.

KEYWORDS

Lithium; bipolar disorder; mood stabiliser; toxicity; emergency.

Lithium has been widely recognised as the first-line treatment for bipolar disorder, with its anti-manic properties first identified in 1949 (Cade 1949; McIntyre 2020). Its primary use is as maintenance therapy in bipolar disorder, being an effective treatment for the prevention of illness recurrence, and in acute episodes of mania and depression (Goodwin 2016; Kessing 2018; Yatham 2018). It has a long history of use in the treatment of depressive disorders, and can be used as augmentation therapy and as prophylaxis for unipolar depression (Cowen 2015). Although an effective treatment, lithium's narrow therapeutic index requires caution with its use, to prevent toxicity. Target therapeutic serum

levels for maintenance therapy in bipolar disorder are approximately 0.6–0.8 mmol/L, but in acute mania higher levels of 0.8–1.0 mmol/L, sometimes up to 1.2 mmol/L, are required (Stokes 1976; Goodwin 2016). As toxicity occurs at concentrations above 1.5 mmol/L, doses are gradually increased with careful monitoring of serum lithium concentrations, and kept at the minimum threshold concentration to achieve therapeutic effect. Once that is achieved, lithium levels are checked on a regular basis.

Lithium's mechanism of action in mood stabilisation remains unclear. It is postulated to modulate glutamate, inositol monophosphate and glycogen synthase kinase 3 pathways in the central nervous system (CNS) and to alter the release of noradrenaline, dopamine and serotonin. The role of lithium's pharmacodynamic properties in intoxication is uncertain (Meyer 2011) and may be an area for future research. However, to understand the pathophysiology of lithium toxicity, the pharmacokinetic properties of lithium must be considered.

Pharmacokinetics

Absorption

When lithium is ingested orally, it is rapidly and completely absorbed by the gastrointestinal (GI) tract within 4–8 h, with serum concentrations of therapeutic doses peaking at 1–2 h after ingestion. Lithium is also available in extended-release formulations, which have limited water solubility and achieve peak serum levels after 5–6 h. Acute ingestion of large quantities of extended-release formulations can result in prolonged absorption, continuous rising of plasma concentrations and peak levels occurring after 48–72 h (Waring 2006).

Distribution

Lithium is an alkali metal and one of the smallest elements in nature. It is therefore easily and rapidly distributed across the total body water (fluid) compartments, with a corresponding volume of distribution of 0.6–0.9 L/kg (Waring 2006; Haussmann 2015). Lithium then begins a slow elimination by the kidneys, and a gradual equilibrium takes place between the intracellular and extracellular compartments.

Lithium distribution is complex and shows preferential uptake in certain compartments, such as the

thyroid and kidney. Lithium concentrations in the brain are similar to those in the plasma. However, distribution of lithium to the brain is delayed by approximately 24 h and peak brain concentrations occur at least several hours later than the serum peak. This must be taken into consideration in cases of lithium intoxication, as toxic neurological symptoms may be seen several hours later than other features as tissue concentration increases (Finley 1995; Waring 2006).

It takes 6 h to allow for the initial distribution of lithium – and accurate interpretation of serum concentration is not possible before this. It is most accurate at 12 h after lithium dosing.

Elimination

Lithium is a simple cation with negligible protein binding and is almost exclusively eliminated by the kidneys. It follows first-order kinetics; the elimination half-life is approximately 20–24 h after a single dose and up to 58 h in chronic use or in the elderly (Timmer 1999; Cates 2005). Lithium is freely filtered by the glomerulus and approximately 80% is reabsorbed, predominantly along the proximal tubule and, to a lesser extent, along more distal tubular segments. Renal clearance in normal individuals is approximately 10–40 mL/min (Okusa 1994). Total body clearance can be impeded by ongoing gastrointestinal absorption, particularly in overdoses of sustained-release preparations (Waring 2006).

Patterns of toxicity

There are three patterns of lithium intoxication, each with their own pharmacokinetics, clinical features and outcomes. These are classified as acute, acute-on-chronic and chronic intoxication.

Acute

Acute intoxication occurs outside of the setting of regular lithium treatment: for example by intentionally overdosing on somebody else's tablets. Acute cases are generally mild, owing to rapid distribution of lithium across body compartments and subsequent falling of serum levels (Jaeger 1993). For this reason, a higher level of lithium is required to cause toxicity in acute cases (Bailey 2000). In comparison with chronic poisoning, the risk of neurotoxicity is low, as lithium concentrations have not yet built up in the brain in acute poisoning (Chen 2004).

Acute-on-chronic

Acute-on-chronic intoxication refers to acute overdose and poisoning in the setting of regular lithium treatment. In contrast to chronic intoxication, acute and acute-on-chronic cases do not tend to show consistent correlation between serum concentrations and clinical features (Bailey 2000).

Chronic

Chronic intoxication, the most common pattern, refers to toxicity over the course of long-term treatment. In chronic intoxication the rate of lithium ingested is greater than the elimination rate, usually over a period of weeks. This may occur due to inappropriately high target concentrations, insufficient monitoring or comorbid illnesses such as chronic kidney disease (Waring 2006).

Acute-on-chronic and chronic cases of intoxication are more likely to display clinical toxicity, as the lithium half-life is longer in these cases (50 h v. 13 h in acute toxicity) (Bailey 2000). This is probably multifactorial and relates to the intracellular lithium accumulation and inhibited lithium efflux with chronic use (Jaeger 1993; Okusa 1994). Patients are therefore exposed to high lithium concentrations for a prolonged period, and longer exposure to elevated lithium concentrations is more toxic than exposure to high concentrations for shorter periods (Chen 2004; Waring 2007). It requires time for lithium to be distributed to intracellular compartments such as the CNS and brain, which occurs with chronic use (Hanak 2015). Further, the rate of lithium elimination exceeds the rate at which it is distributed out of intracellular sites such as the brain – a phenomenon that is more evident with chronic treatment. Chronic toxicity has increased risk for neurotoxicity and a worse prognosis in comparison with acute intoxication (Chen 2004). It is unclear whether higher lithium concentration affects renal clearance of lithium, or whether reduced renal clearance causes higher concentration (Bailey 2000).

Epidemiology

There are few population-based studies reporting on rates of lithium toxicity. A case–control study identified a prevalence rate of 2% for lithium toxicity over a 5-year study period (Heath 2018), whereas a large Swedish population-based study identified a rate of 7% over a 17-year period (Ott 2016). Lithium intoxication is a common occurrence over several years of treatment but annual incidence remains low, with an incidence rate of 1/100 lithium-treated patients developing intoxication per year of lithium treatment in the Swedish observational study (Ott 2016).

Across various studies, intoxication occurs nearly twice as frequently in women. Chronic intoxication is the most common pattern (Offerman 2010; Ott 2016). In general, the incidence of acute-on-

TABLE 1 Patterns of lithium intoxication among individuals requiring hospital admission

	Acute intoxication	Acute-on-chronic intoxication	Chronic intoxication
Prevalence[a]			
Canada (5-year period) (Offerman 2010)	9%	25%	56%
Sweden (17-year period) (Ott 2016)	1.2%	25.3%	59.4%

Clinical risk factors	History of overdose
	  Dehydration
	  Decline in renal function secondary to gastrointestinal illness
	  Lithium increase secondary to NSAIDs, ACE inhibitors
			Clinical diagnosis with levels to confirm long-standing lithium use
			  Renal impairment, e.g. chronic kidney disease, NDI
			  Concurrent illness
			  Dehydration
			  Lithium increase secondary to NSAIDs, ACE inhibitors

Clinical features	Early gastrointestinal symptoms: nausea, vomiting, diarrhoea
	  Cardiac and renal features
	  Neurological features (may occur late)
			Early neurological features, most commonly altered level of consciousness
			  Cardiac and renal features

Investigations	Serum lithium concentration elevated
	  May not correlate with toxicity
	  Normal concentration does not rule out diagnosis
			Serum lithium concentrations correlate with clinical picture of toxicity

NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin-converting enzyme; NDI, nephrogenic diabetes insipidus.a.. Prevalence where the pattern of intoxication was unknown was 10% in the Canadian study and 14.3% in the Swedish study.Sources: Bailey & McGuigan, 2000; Waring et al, 2007; Offerman et al, 2010; Ott et al, 2016.

chronic intoxication may be underestimated, with one survey identifying this category as the most frequent (Bailey 2000). Although acute intoxication accounts for the least common pattern of intoxication (Mowry 2014), a prospective evaluation of referrals to a national poisons centre in Scotland found this category to be the most frequently reported (Waring 2007). Table 1 shows the prevalence of the various patterns of intoxication among individuals requiring hospital admission in a Canadian study over a 5-year period (Offerman 2010) compared with Swedish observational data (Ott 2016).The mortality rate is 0.8% (Offerman 2010), a significant improvement in comparison with the mortality rate in the 1970s, which was reported at 15% (Hansen 1978).

Aetiology

Lithium intoxication may be the result of several different risk factors (Table 2). Medications such as thiazide diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) interact with lithium and increase its serum concentration by reducing its renal clearance. As a monovalent cation, lithium resembles sodium in size and charge. In states of sodium depletion or sodium avidity (e.g. extracellular volume depletion due to vomiting or diarrhoea), the proximal tubular absorption of lithium increases, therefore increasing the risk of lithium toxicity. Both thiazide diuretics and NSAIDs alter renal lithium clearance by triggering increased

tubular reabsorption of sodium (and lithium). In the case of thiazide diuretics, this occurs in response to the natriuresis caused by the drug. In the case of NSAIDs, it is postulated to be due to the inhibition of prostaglandin production, which decreases renal blood flow, promoting sodium avidity (Finley 1995, 2016).

Chronic renal impairment and nephrogenic diabetes insipidus (NDI) are important risk factors to consider, as they both occur commonly in the setting of long-term lithium treatment (Gupta 2013). Impaired urinary concentrating ability is seen in up to 40% of patients on lithium, and approximately 12% develop NDI (Stone 1999; Gupta 2013). The cause is multifactorial, involving lithium's interference with the effects of anti-diuretic hormone (ADH), aquaporin-2 synthesis and prostaglandin production. This is usually reversible during the first 6 years of treatment but may become permanent with long-term treatment ($\geq$15 years) and may result in NDI (Grandjean 2009; Gupta 2013). Whether lithium intoxication itself has long-term effects on renal function remains uncertain and represents a potential avenue for further research (Ott 2016).

Clinical features

Lithium intoxication has a heterogeneous clinical presentation with varying clinical features, from asymptomatic to clinical signs of severe toxicity. Any lithium-treated patient who develops altered

TABLE 2 Risk factors in lithium intoxication

Risk	Causes/characteristics

Reduced clearance of lithium	Concurrent medication use, e.g.:
	    NSAIDs
	    ACE inhibitors
	    Thiazide diuretics
	Decreased extracellular volume due to:
	    gastrointestinal losses (vomiting/diarrhoea)
	    reduced fluid intake
	    high insensible losses, e.g. fever, severe burns
	    diuretic medication
	    major haemorrhage/blood loss
	Decreased effective arterial volume due to:
	    cirrhosis
	    congestive heart failure
	    sepsis
	Renal impairment due to:
	    chronic kidney disease
	    nephrogenic diabetes insipidus

Increased ingestion of lithium	Intentional overdose Longer term lithium use

Medical misadventure	Inappropriately high target lithium concentrations
	    Inadequate monitoring of lithium levels
	    Inadequate psychoeducation

Patient factors	Female gender
	    Increased age (>50 years)
	    Alcohol use
	    Thyroid dysfunction: hyper- and hypothyroidism; hyperparathyroidism

Sources: Okusa & Crystal, 1994; Oakley et al, 2001; Webb et al, 2001; Bedford et al, 2008; Haussmann et al, 2015; Baird-Gunning et al, 2017.

level of consciousness, vomiting, gross tremor or cerebellar signs should be considered to have lithium intoxication and managed as such until the situation is clarified.

The CNS is the most significantly affected system in lithium toxicity, and altered level of consciousness is the most commonly reported feature (Offerman 2010). CNS features include drowsiness, coarse tremor, slurred speech, hyperreflexia, agitation, muscle weakness and ataxia. With increasing severity, increased confusion, disorientation and seizures may occur, progressing to more impaired levels of consciousness and eventually coma (Jaeger 1993; Bailey 2000; Ott 2016). Gastrointestinal features include nausea, vomiting and diarrhoea. Renal symptoms of polyuria and polydipsia occur, and impaired urinary concentrating ability is seen in acute intoxication (Erden 2013). Acute renal failure occurs rarely (Gupta 2013). Cardiac features also develop, including bradycardia, prolonged QTc intervals, arrhythmias and, in severe cases, cardiovascular collapse (Bailey 2000).

Other neurological manifestations occasionally seen include extrapyramidal features, generalised polyneuropathies and neuromuscular features such as fasciculations and myoclonus (Grandjean 2009). Most symptoms and signs of lithium intoxication resolve as serum lithium levels normalise, but there is a risk of long-term neurological sequelae such as the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT), which predominantly manifests as cerebellar dysfunction, with features of ataxia, dysarthria and dysmetria (Adityanjee 1987).

There may be differences in the clinical presentation depending on which pattern of lithium toxicity has occurred. Individuals with acute toxicity are more likely to be asymptomatic, despite high lithium concentrations, and gastrointestinal symptoms are thought to occur earlier and more frequently. By contrast, chronic toxicity is predominantly associated with gradually developing neurological signs and may present with overt signs and symptoms despite relatively low lithium levels (Timmer 1999; Grandjean 2009).

Differential diagnosis

The differential diagnosis (Box 1) includes a range of presentations associated with neurological features and alterations in mental status or levels of consciousness. It is essential to rule out neuroleptic malignant syndrome (NMS) and serotonin syndrome. Both may occur in the setting of lithium treatment and may have fatal outcomes. Lithium toxicity, NMS and serotonin syndrome can all present with altered consciousness and neurological features. NMS will be distinguishable by fever >38°C, generalised (lead-pipe) rigidity, bradykinesia and autonomic instability, along with raised creatinine

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BOX 1 Differential diagnosis

Iatrogenic effect

Psychotropic medication-related adverse event:

- serotonin syndrome
- seuroleptic malignant syndrome

Intoxication

Drug toxicity, e.g. due to:

- anticholinergics
- cocaine
- phencyclidine (PCP)

Withdrawal syndrome, e.g. due to:

- alcohol
- benzodiazepines

Endocrine dysfunction

Thyroid dysfunction:

- thyrotoxicosis
- hypothyroidism

Glucose disturbance:

- hypoglycaemia

Neurological effect

Trauma, e.g. head trauma

Infection, e.g. central nervous system infection

Vascular, e.g. cerebrovascular accident

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BOX 2 Key clinical factors to assess in lithium intoxication

- Acute ingestion or not
- Time course: acute, acute-on-chronic, chronic
- Signs and symptoms and time since onset
- Time since acute ingestion
- Time of last lithium intake
- Regular lithium dose and duration of use
- Lithium dose changes
- Formulation: extended-release versus immediate-release
- Prior lithium concentration measures (if available)
- Medical conditions (Table 2): e.g. chronic kidney disease, nephrogenic diabetes insipidus
  (Grandjean 2009; Haussman 2015; Baird-Gunning 2017)

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kinase. Distinguishing features of serotonin syndrome include agitation, shivering, diarrhoea, hyperreflexia of the lower limbs, and myoclonus (including ocular clonus) (Gupta 2013; Wadoo 2021).

Assessment and management

Recognition

The first step in the management of lithium intoxication is prompt recognition and early referral for medical intervention. Clinicians must be vigilant and screen for toxicity symptoms as well as for risk factors for intoxication. Both patient and clinician may miss early features of intoxication, and therefore continuous psychoeducation is essential. An awareness of potentially fatal outcomes of lithium intoxication is necessary, with increased risk in cases of chronic and acute-on-chronic intoxication.

Referral

When lithium toxicity is suspected, blood tests including serum lithium concentration and renal function should be performed. Generally, a referral

to hospital may be indicated to allow for the timely completion of tests (Haussmann 2015).

Box 2 shows key clinical factors to assess in each case of lithium intoxication, which will influence management and monitoring requirements. In cases of overdose, additional drug ingestion must be clarified.

Investigation

Serum lithium concentration should be measured on presentation. Clinical findings of toxicity commonly occur at serum concentrations >1.5 mmol/L (Ott 2016). However, serum lithium concentrations should only be viewed as a guide to potential toxicity and must be interpreted in relation to the clinical findings and renal function.

Serum lithium concentration measurements should be repeated every 2–4 h during initial management. Once they are decreasing they can be checked 6–12 hourly (Haussmann 2015). Table 3 provides a list of recommended investigations.

Serial lithium measurements are necessary owing to lithium's delayed distribution to the CNS and brain. Serial concentrations are also useful for determining the type of intoxication that has taken place: a level that peaks and quickly falls suggests acute intoxication, whereas levels that persist or rebound indicate chronic saturation of the tissues (Haussmann 2015). Serial testing is also required in cases of overdose of sustained-release lithium to establish the extent of toxicity that has taken place (Grandjean 2009).

Renal function is important as this may be disturbed in lithium toxicity, which can prolong the clearance of lithium and exposure to toxic levels (Grandjean 2009). Persistent electrolyte

TABLE 3 Investigations in suspected lithium toxicity

	Investigation	Notes
Bedside	Vital signs	Temperature: hypo- or hyperthermia
		Blood pressure: hypo- or hypertension
		Oxygen saturation
		Respiratory rate: respiratory depression
	Pregnancy test	In women of childbearing age
	Glucose	Fingerstick
Bloods	Lithium concentration (may not correlate with clinical severity)	On presentation
		Every 2–4 h during treatment
		6–8 h after dialysis
		12 h after completion of dialysis
	Urea and creatinine	Every 12–14 h
	Sodium	Every 6–12 h
		More frequently if:
		symptomatic hyponatraemia
		nephrogenic diabetes insipidus
		abnormal sodium on initial testing
	Electrolytes	Potassium
		Calcium
		Magnesium
	Anion gap	May be low owing to high serum lithium concentrations (>4 mmol/L)
	Urine specific gravity	
	Thyroid-stimulating hormone (TSH)	Thyrotoxicosis
		Hypothyroidism
	Other toxicology – in case of co-ingestion	Paracetamol level
		Salicylate
Cardiology	Electrocardiogram (ECG)	QTc prolongation
		Atrioventricular (AV) block
		T-wave flattening
		Bradycardia

Sources: Decker et al, 2015; Haussman et al, 2015; Gitlin et al, 2016; Baird-Gunning et al, 2017.

disturbances may require an intensive care unit (ICU) admission.

Treatment

Admission

Hospital admission should be considered for individuals with clinical signs and symptoms of toxicity (this should be instigated regardless of lithium concentration, as serum levels may not correlate with degree of neurological symptoms) and for those with a serum level >2.0 mmol/L on a background of chronic lithium treatment. Approximately 80% of individuals with lithium intoxication require admission (Offerman 2010), with an emphasis on stabilising the patient and minimising the time of exposure to toxic lithium levels (Decker 2015).

Admission to an ICU is required if there are severe and life-threatening symptoms such as cardiovascular collapse, respiratory depression, severe neurological symptoms, hyperthermia requiring immediate cooling, or renal failure, or if there are very high lithium concentrations (>4.0 mmol/L). Intubation is required in approximately 5% of patients with lithium intoxication (Offerman 2010).

Stabilisation

In all cases, initial management is as with any case of poisoning, using an ABCDE (airway, breathing, circulation, disability, exposure) approach to achieve airway management, ensuring adequate breathing and oxygen saturation, and circulatory support.

Medication review

In cases of mild toxicity, discontinuation of lithium may be all that is required.

It is essential to remove any medications that may be exacerbating lithium intoxication by pharmacokinetic interactions limiting renal excretion, such as NSAIDS, angiotensin-converting enzyme (ACE) inhibitors and diuretics, and medications with pharmacodynamic interactions with increased risk of neurotoxicity or cardiovascular adverse effects. Any medications potentially contributing to symptoms of toxicity should be reviewed and discontinued if safe to do so. This includes any medication that may also cause cardiac arrhythmias or QTc prolongation, neurotoxicity (e.g. antiepileptics) or electrolyte imbalance.

Fluid resuscitation

In chronic cases of toxicity, dehydration and volume depletion is a frequent cause. Fluid infusion with normal saline is required to correct and/or prevent

volume depletion and restore electrolyte and fluid balance (Grandjean 2009). This should occur alongside regular monitoring of serum sodium concentration to monitor for hypernatraemia. Hypernatraemia may occur when there is an inadequate level of intravenous hydration and a lack of access to free water intake in someone with NDI or impaired urinary concentrating ability secondary to lithium. If this occurs, replacement of the calculated total body water deficit is required, using normal or hypotonic saline (Stone 1999).

Acute intoxication

Absorption preventive measures are used in acute intoxication only, and include gastric lavage and whole-bowel irrigation.

Gastric lavage

There is limited evidence to support the use of gastric lavage, but it may be helpful if administered within 1 h of ingestion (Teece 2005; Waring 2006).

Whole-bowel irrigation

Whole-bowel irrigation with polyethylene glycol solution is considered when acute poisoning by extended-release formulations occurs, with recommendations for use when at least 80 mg/kg of lithium are ingested. It should be initiated within 12 h of ingestion (Wilting 2009) in alert patients with no confusion allowing the patient to drink the solution or for nasogastric tube insertion to allow for the rapid ingestion of the fluid (1–2 L/h) until there is clear rectal effluent. However, this intervention is also based on limited evidence and caution is required as it may cause hypokalaemia (Reumkens 2017). Bowel obstruction or haemodynamic instability would be contraindications to the use of whole-bowel irrigation.

Forced diuresis

Forced diuresis is the administration of intravenous fluid, sometimes along with diuretics, to enhance renal clearance of medication. Although potentially helpful in patients with volume depletion, it is no longer used and is in fact contraindicated owing to a lack of evidence for its efficacy and as it may exacerbate water and electrolyte imbalance (Waring 2006).

Activated charcoal

Activated charcoal has no effect on lithium toxicity, but may be helpful in cases of polysubstance intoxication (Okusa 1994).

Dialysis

In severe cases, treatment should be commenced with extracorporeal treatments (ECTRs). ECTRs used in toxin removal include intermittent haemodialysis, continuous renal replacement therapies (CRRTs) and, to a lesser extent, peritoneal dialysis. Solute removal from the intravascular compartment can occur by diffusion or convection (or both) (Decker 2015). In a large study of lithium intoxication cases, 14% of patients received haemodialysis, 71% of whom had chronic intoxication (Offerman 2010).

Owing to its physical and pharmacokinetic properties, lithium is very effectively and rapidly dialysed (Okusa 1994). Clinical guideline recommendations for the initiation and cessation of dialysis are inconsistent, but because of the risk of permanent neurological sequelae with lithium toxicity, the decision to initiate haemodialysis should be made in the first 8–12 h of admission (Timmer 1999). There is a lack of randomised trial data on which to base treatment decisions, and further contributing to the inconsistency in clinical guidelines is the heterogeneity of clinical presentations, differing categories of intoxication and the lack of correlation between serum concentrations and clinical toxicity, particularly in acute scenarios.

Recommended indications for haemodialysis are displayed in Table 4. These recommendations are based on guidelines developed by the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup via expert consensus (Decker 2015) and take more of a clinical approach than previous guidelines, which suggested haemodialysis for serum lithium levels >4 mmol/L in acute toxicity and >2.5 mmol/L in chronic toxicity (Baird-Gunning 2017). Patients falling outside of the categories listed in Table 4 need careful consideration on a case-by-case basis, which will be guided by the lithium absorption, distribution and elimination factors in each case (Grandjean 2009). This will be informed by the type of toxicity that has taken place, the formulation of lithium involved and clinical features such as comorbid illnesses preventing extensive intravenous hydration (Haussmann 2015). Haemodialysis is also recommended for those with serum levels that continue to rise owing to continued gastrointestinal absorption. A suggested guide to determine efficacy has been described as attainment of serum levels <1.0 mmol/L 6–8 h after dialysis (Waring 2006; Decker 2015).

Rebound of serum lithium levels is seen 6–12 h after haemodialysis, as lithium is redistributed from deeper tissue compartments to the plasma (Okusa 1994; Decker 2015). Therefore, accurate assessment and appropriate treatment should take place within this period (Dawson 1999). It is

TABLE 4 Indications for dialysis

Clinical features	Clinical context
Serum lithium concentration Li$^+$ >5 mmol	Irrespective of clinical features
Li$^+$ >4 mmol	With renal impairment present
Expected time to achieve Li$^+$ <1 mmol is >36 hours	Irrespective of clinical features
Signs of severe intoxication: decreased level of consciousness, neurological features, life-threatening dysrhythmias	Irrespective of Li$^+$

Sources: Decker et al, 2015; Baird-Gunning et al, 2017.

recommended that the lithium concentration should be measured 6 h after haemodialysis to check that levels are decreasing. An increase in serum lithium concentration of >1.0 mmol/L within 8 h of dialysis is a recommended indication for repeat dialysis (Baird-Gunning 2017), and dialysis should be repeated until serum lithium concentrations are <1 mmol/L for at least 6 h after treatment and there is also clinical improvement (Okusa 1994; Decker 2015). It is often the case that clinical improvement is slower than reductions in lithium concentrations. Studies have indicated that at least two haemodialysis treatment courses may be required to treat lithium intoxication (Okusa 1994).

Dialysis modality
Intermittent haemodialysis

Intermittent haemodialysis is the most rapid and effective way of clearing lithium from the plasma. It utilises ultrafiltration for fluid removal and uses predominantly diffusion for solute removal. Depending on blood flow, haemodialysis can achieve a lithium clearance of up to 180 mL/min (Bouchard 2014). Although intermittent haemodialysis is well tolerated in most patients, it can cause haemodynamic compromise in individuals with cardiovascular instability such as cardiac arrhythmia or hypovolaemic or septic shock. Patients require close haemodynamic monitoring and may require inotropic or vasopressor support during dialysis.

Continuous renal replacement therapy

Continuous renal replacement therapies such as continuous arteriovenous haemodiafiltration (CAVHD) and continuous venovenous haemodiafiltration (CVVHD) may also have a role as second-line extracorporeal treatments; they clear lithium at a rate of 20–40 mL/min (Decker 2015; Waring 2006). In comparison with intermittent haemodialysis, these methods of ECTR are slower and occur over a longer period. CRRT utilises diffusion, convection or both for solute removal (Jha 2018). CRRT is helpful for patients who are haemodynamically compromised or for whom there may be a delay in initiating haemodialysis (Waring 2006).

Peritoneal dialysis

Peritoneal dialysis may be considered if haemodialysis or CRRT are contraindicated or delayed (Waring 2006). This method is significantly less effective, with lithium clearance rates only marginally higher than that of renal clearance, at 9–14 mL/min (Brown 1981).

Discharge criteria

Once the patient has been treated and stabilised, and lithium effectively eliminated, discharge from hospital can be considered. Our recommendation is that this can be safely done once clinical improvement occurs and serum lithium levels have been <1.5 mmol/L for 1–2 days. However, in cases of large-volume ingestion of sustained-release preparations of lithium, it may be necessary to continue to observe for 3–4 days (Timmer 1999). Considerations can then be made as to whether to restart lithium.

Restarting lithium

Individuals who have previously responded well to lithium with no contraindications to restarting treatment should have their lithium reintroduced when it is safe to do so. This should be a multidisciplinary team decision, with the patient's involvement, taking the risks and benefits of continued lithium treatment into account. Risks to consider include the risk of acute overdose, the risks with medical comorbidities such as chronic kidney disease and NDI, and the likelihood of future lithium intoxication (Baird-Gunning 2017). These must be weighed against the benefit of maintenance lithium therapy in bipolar disorder.

To date, there are no guidelines on the reintroduction of lithium after lithium intoxication and evidence remains lacking in this area. Our recommendation is to restart treatment once serum lithium levels have been within, or below, the therapeutic range for at least 24 h.

Psychoeducation is crucial in those recommencing treatment, with a view to preventing recurrence of intoxication. Careful dose titration and monitoring of serum levels is required. There may be a need to reassess target lithium concentrations given the patient's longitudinal history and comorbidities. Medications that interact with lithium to increase toxicity risk should be discontinued. Patients must also be counselled on the long-term risk of irreversible neurological sequelae (Adityanjee 1987).

Conclusions

Lithium intoxication, although potentially life-threatening, can be safely managed in most cases and the mortality rate is low. There are few studies reporting on the prevalence and incidence of lithium intoxication, but its relatively low incidence suggests that current lithium monitoring procedures are effective in minimising risk of lithium toxicity. In cases of suspected lithium intoxication, clinical features of lithium toxicity are more important than serum lithium levels, and any lithium-treated patient who develops vomiting, confusion or cerebellar signs should be assumed to have lithium toxicity until the situation is clarified. Clinicians should have a low threshold to check lithium levels if clinical features of concern occur.

There is no specific antidote for lithium intoxication. The pattern of lithium exposure and subsequent intoxication category have important implications for management and prognosis.

Many treatment approaches are available, but randomised trial data regarding their efficacy are lacking. The mainstay of treatment is stabilisation of the patient and minimisation of the time of toxic exposure to lithium. More trial data are required to better establish specific criteria for treatment interventions, to clarify when to initiate specific interventions such as dialysis, and to better determine differential treatment outcomes. Clear guidelines do not yet exist regarding when to restart lithium and when to discharge from hospital following intoxication. Prevention of lithium intoxication is crucial, and education of clinicians and patients is key to ensuring that risk factors for intoxication are minimised and clinical features are recognised early.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

All authors contributed to the writing of the manuscript. J.L. conceived the idea of the article and oversaw the project. N.M. carried out a literature review and did the primary writing of the article.

Declaration of interest

None.

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MCQs

Select the single best option for each question stem

1 The following features are risk factors for lithium toxicity except:
a dehydration
b NSAIDs
c chronic kidney disease
d epilepsy
e female gender.

2 Gastrointestinal symptoms are most commonly seen:
a in acute lithium toxicity
b in acute-on-chronic lithium toxicity
c in chronic lithium toxicity
d in all forms of lithium toxicity
e as a normal side-effect of therapeutic lithium.

3 The following are used in the management of lithium toxicity except:
a correction of dehydration and sodium depletion
b activated charcoal
c discontinuation of lithium
d gastric lavage
e haemodialysis.

4 The most effective way of eliminating lithium from the serum is:
a continuous renal replacement therapy
b whole-bowel irrigation
c haemodialysis
d peritoneal dialysis
e fluid resuscitation.

5 Recommended indications for haemodialysis in lithium intoxication include all except:
a serum lithium levels >5 mmol/L
b serum lithium levels >4 mmol/L with renal impairment
c if the expected time to achieve serum lithium level <1 mmol is >36 h
d severe clinical features regardless of toxicity
e ingestion of extended-release lithium.