Lithium toxicity: the importance of clinical signs

Although there appears to be a decline in its use, lithium is still used extensively in the UK to treat bipolar disorder. However, lithium can be quite toxic and lead to long-term problems, rarely death. Therefore, doctors need to carefully monitor patients taking lithium and seek appropriate advice whenever concerns are raised.

Following its discovery over 190 years ago, lithium was mainly used initially for the treatment of gout in the 1800s, and by the early 1900s had become popular as a panacea for all sorts of ailments, in the form of mineral spring waters. A disastrous period of use for the treatment of hypertension and heart disease in the USA led to lithium products being removed from the market because of reports of toxicity and death. Lithium was rediscovered in 1949 by John Cade and became recognized as a potential treatment for 'psychotic excitement'. Cade observed that a lithium urate solution had noticeable effects on guinea pigs, causing them to become lethargic and unresponsive to stimuli for 1–2 hours. Since then lithium (usually in the form of the carbonate salt) has been used for the treatment and prophylaxis of bipolar disorder, particularly the hypomanic phase, and as an adjunct in treating depression.

Pharmacology and physiology

Lithium is usually prescribed orally in tablet form as the colourless carbonate salt (Li_2CO_3), or as a liquid preparation of lithium citrate. As a rough guide, a 400 mg tablet of lithium carbonate contains 10.8 mmol lithium (Taylor et al, 2005). When given orally, complete absorption from the gastrointestinal tract occurs usually within 8 hours (absorption may vary) and serum levels generally peak between 1 and 6 hours, a few hours later for sustained-release preparations.

The half-life of 12–24 hours tends to increase with age (up to 36 hours), and the manner in which lithium is taken, for example acute-on-chronic ingestion (i.e. taking extra lithium while on maintenance treatment) *vs* chronic. Levels sometimes continue to rise for 3 or 4 days in a few patients. The distribution of lithium to the brain, determined by magnetic resonance spectroscopy, is characterized by delayed uptake and elimination when compared with serum levels and the concentration in CSF is about 50% of plasma levels. Many patients take lithium as a single dose at bedtime and morning lithium levels may be higher than with twice-daily dosing. Therefore, following a potentially toxic dose, serum lithium levels should be interpreted relative to the time lithium was ingested.

The optimal steady-state concentration of lithium for maintenance treatment of bipolar disorder is generally considered to be 0.6–1.0 mEq/litre (mmol/litre). However, lithium has a narrow therapeutic window and toxicity sets in usually when plasma levels go beyond 1.5 mEq/litre. Serum concentrations above 3 mEq/litre are often associated with severe symptoms and generally require haemodialysis. Unfortunately, toxic symptoms may be present even when concentrations are well within the recommended therapeutic range and although toxicity is generally correlated with serum drug concentrations, there is great variability in severity associated with a given concentration. Management should therefore be dictated both by the patient's presentation and serum levels.

Lithium is present in insignificant amounts in body fluids (less than 0.2 mEq/litre) and has no known physiological role in the body. Its mechanism of action is not well understood. It is thought to stabilize mood by decreasing neuronal responsiveness to neurotransmitters, the result of modifying second messenger systems such as the phosphoinositide cycle. Lithium is not significantly bound to plasma proteins and because of slow movement of lithium from the extracellular to intracellular space, steady-state concentrations and the desired therapeutic effect take some 6–10 days to achieve. The highest concentrations of lithium are found in the kidney and brain where lithium exerts most of its toxic effects.

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in faeces; renal excretion is proportional to its plasma concentration. About one third of the total body water is extracellular and initially lithium is distributed in the extracellular fluid (comprised of interstitial fluid and blood plasma). A generally accepted value for extracellular fluid volume is 20% of the body weight, or about 14 litres in an averaged-sized individual (Ganong, 2005). The excretion rate does not vary unless there are mitigating factors.

Effects on renal function

Lithium is excreted almost entirely as a free ion by the kidneys and approximately 60–80% of filtered lithium is reabsorbed in the proximal tubule mainly (in a way

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similar to sodium), and a further 20% is reabsorbed between the loop of Henle and the collecting duct. It is freely filtered by the glomerulus since it is not bound to serum proteins. In the proximal tubule lithium is handled similarly to sodium. Factors that decrease glomerular filtration rate or increase proximal tubule reabsorption, such as volume depletion, will lead to an increase in serum lithium levels. Conversely, factors that decrease proximal tubule sodium reabsorption, such as carbonic anhydrase inhibitors, tend to reduce lithium levels. Reduction in prostaglandin E2, caused by non-steroidal anti-inflammatory drugs, results in a reduction in renal blood flow and an increase in the reabsorption of sodium and lithium (Faaij et al, 2009). Thus, most physicians would agree that angiotensin-converting enzyme inhibitors, diuretics and non-steroidal anti-inflammatory drugs should be prescribed with extra care, especially in elderly patients taking lithium, because of their potential to cause lithium toxicity.

Side effects

Side effects are common within the normal plasma range and occur in about 80% of patients. Fortunately, they are minor and usually transient, but nonetheless annoying (*Table 1*). Weight gain is troublesome for many patients (up to 10 kg in some cases); gastrointestinal symptoms (nausea and/or diarrhoea in about 30% of patients), or a fine tremor, often responsive to propranolol treatment, are frequently seen. Mild polyuria occurs early and tends to disappear. In most patients initial side effects are usually tolerated, meaning patients can be maintained on the same dose. Acne and psoriasis may be triggered or exacerbated. Care should be taken with breast feeding as lithium passes freely from maternal plasma to breast milk and concentrations reach 50% that of the former, with the potential risk of causing hypotonia in the infant. In practice, doctors tend to adjust the dose of lithium on the basis of tolerance, side effects, previous blood reports and general physical condition, while maintaining levels within the therapeutic range.

Effects on cerebral function

Although not generally sedating, some patients complain of feeling lethargic and slowed down, which may not be surprising as some hypomanic patients enjoy the elated mood. Symptoms usually associated with moderate toxicity include lethargy, inertia, drowsiness, coarse hand tremor, muscle weakness and vomiting. A corroborative history from family and others should help clarify alterations in the patient's presentation, as terms such as lethargy and inertia are vague, and could also be symptoms of a change from elation to depression.

With mild toxicity the lithium dose usually needs to be reduced, and where patients find the side effects too unpleasant, they will need to be switched to another mood stabilizer. Moderate poisoning should be easier to identify, being associated with confusion (impairment of attention and consciousness), dysarthria, nystagmus, ataxia, myoclonic twitches and electrocardiogram changes (flat or inverted T waves). Severe toxicity is associated with grossly impaired consciousness, increased deep tendon reflexes, seizures, syncope, renal insufficiency, coma and death.

There will invariably be some overlap in many cases, for example, nausea and drowsiness can occur with all grades of toxicity. Other ominous symptoms of toxicity include light-headedness, slurred speech, tinnitus and blurred vision. States of reduced alertness vary from drowsiness, stupor and coma. Drowsiness and stupor are usually attended by some degree of confusion; with coma, the patient cannot be aroused. A description of the level of arousal and of the type of responses evoked by various stimuli, precisely as observed at the bedside, is preferable to ambiguous terms such as lethargy (Harrison, 2008). The neurological Glasgow Coma Scale will give a reliable method of assessing a patient's level of consciousness, should this problem arise, when patients are admitted to hospital. With moderate or severe poisoning, lithium needs to be stopped immediately.

Patterns of toxicity

Essentially there are three ways in which lithium poisoning occurs. Acute poisoning occurs in individuals not being treated with lithium, for example, children who have accidentally taken tablets prescribed for another member of the family. Acute poisoning can also occur as a suicide attempt. This form of toxicity generally carries less risk, and patients tend to have milder symptoms because the elimination half-life is shorter in patients

Table 1. Adverse effects of lithium

Sign		Management
Mild toxicity	Fine hand tremor	Decrease lithium dose, try twice-daily dosage, or switch to an alternative mood stabilizer
	Diarrhoea, nausea	
	Polyuria and thirst	
	Weight gain	
	Inertia	
	Lassitude	
Moderate toxicity	Coarse hand tremor	Stop lithium: monitor levels and urea/electrolytes
	Confusion	
	Nystagmus	
	Dysarthria	
	Ataxia	
Severe toxicity	Seizures	Admit to intensive care unit
	Syncope	
	End-stage renal failure	
	Coma, eventually death	

who have never taken lithium. Nonetheless, frequent lithium levels should be carried out and haemodialysis considered if renal function has been compromised.

Acute-on-chronic poisoning occurs usually in bipolar patients who have overdosed on their prescribed lithium, whether by accident or intent. This form of toxicity is generally more severe because the elimination half-life tends to be prolonged. Chronic toxicity (most cases) occurs in patients receiving long-term lithium when the lithium dose has been increased, or in individuals whose renal function is or has become impaired. The severity of long-term toxicity correlates directly with the serum lithium concentration and may be broadly categorized as mild (1.5–2.0 mEq/litre), moderate (2.0–2.5 mEq/litre) or severe (>2.5 mEq/litre).

Plasma levels should be taken 12 hours after the last dose of lithium because the trough, not the peak concentration, determines the daily dose. There may be a lesser risk of renal damage when lithium is given as a single night-time dose, perhaps because lithium levels are not as prone to fluctuations, and polyuria less frequent than when lithium is given as a twice-daily dose. In addition, side effects are less troublesome at nighttime and compliance better. Excretion in the urine is rapid during the first 6–8 hours and slow thereafter for about 10–14 days; a steady state of urinary excretion is eventually reached after about 2–3 weeks. Conversely, when lithium treatment is discontinued, there is an initial rapid phase of excretion followed by a 10–14-day elimination phase (Goodman and Gilman, 1990). Once a patient is stabilized on lithium its pharmacokinetics allow lithium to be given regularly with relative safety. Life-threatening lithium toxicity tends not to occur below serum levels of 3.0 mmol/litre. About 10% of patients exposed to elevated lithium levels for prolonged periods may endure permanent damage to the cerebellum and basal ganglia.

Clinical signs are the most important means of detecting intoxication: serum levels should be taken for confirmation. Always bear in mind that toxicity may occur even when lithium levels are within the therapeutic range, so there may be a false sense of security initially. Also, excessive exercise or games, particularly in hot, humid conditions, diarrhoea, and severe dieting, may lead to greater fluid loss and subsequent increased lithium concentration. Should toxic symptoms develop later it may be not be possible to avoid permanent sequelae. Fortunately, death is rare, even after large overdoses.

Clinical observation should take priority and any evidence of the above symptoms automatically requires a lithium level reading. Other possible risk factors for lithium toxicity at normal serum levels include rapid dosage regimens, pre-existing electroencephalogram abnormalities, a genetic predisposition and underlying organicity (Bell et al, 1993). The elderly and those patients with pre-existing neurological or other general diseases (especially with fever) are at increased risk. In elderly patients, lithium toxicity may present atypically, for example following a fall, or with a confusional state. Because lithium competes for sodium, decreased sodium reabsorption by the renal tubules leads to hyponatraemia. It is essential therefore for patients to maintain a normal diet, including salt, and an adequate fluid intake (2–3 litres daily at least) during the initial stabilization period.

Other adverse factors

Because of the manner of its distribution into body tissues, lithium can accumulate in cells even when serum levels are falling. Conversely, a high serum lithium level does not necessarily imply toxicity, and although concerns should be raised, organic damage may not necessarily ensue. Elevated levels have been noted with normal therapeutic doses when lithium is collected in the wrong tube, for example, one preserved with lithium heparin. GPs commonly prescribed diuretics for patients with hypertension and/or ankle oedema, and these cause hypovolaemia via increased sodium excretion, resulting in a raised serum lithium concentration.

The other main concern of prolonged lithium treatment is that of renal damage, as there have been reports of interstitial fibrosis and focal necrosis with continued lithium treatment. Alcohol increases lithium concentration, possibly because it promotes diuresis. Fortunately, various other signs mentioned above are often present, alerting the physician to take appropriate action. In acute overdose mortality is reported to be about 25%, and 9% in patients receiving lithium for maintenance treatment. Lithium levels fall on average by 0.2 mmol/litre 12–24 hours after an initial dose.

The main adverse renal effect of lithium is nephrogenic diabetes insipidus (which occurs in 20–40% of patients) and presents as polyuria and polydipsia, possibly as a result of reduced levels of the membrane protein aquaporin-2, the collecting duct water channel found in renal tubular cells, or to down-regulation of antidiuretic hormone receptors. Aquaporins (water channels), as the name suggests, facilitate the transport of water across cell membranes by a process of simple diffusion. Interference with the function of aquaporins therefore leads to problems with water reabsorption, and hence diabetes insipidus. Lithium also interferes with the ability of antidiuretic hormone to increase water permeability. Proteinuria is uncommon with lithium and the nephrotic syndrome rare. The impairment of renal concentration is not of particular importance as such, but prolonged polyuria leading to dehydration is another matter, as is the risk of hypokalaemia. The latter can be minimized by treatment with potassium-sparing diuretics such as amiloride.

Cardiac complications are less often seen with acute lithium toxicity than with chronic ingestion. Nonetheless, electrocardiogram changes such as T-wave inversion and flattening, first-degree atrioventricular conduction delay, ST segment depression, prolonged QT interval and, rarely, ventricular arrhythmias are all recognized side

effects. The oft-quoted Epstein's anomaly (described in 1866) characterized by displacement of the tricuspid valve leaflets, is uncommon, occuring in 1 per 1000 births in pregnant women using lithium. It is associated with the ingestion of lithium during pregnancy, the risk being greatest at 2–4 weeks, and causes mild to severe tricuspid regurgitation. Sinoatrial block may be related to lithium's competitive inhibition of calcium in the Na+/Ca2+ exchange in cardiac cells.

For some unknown reason, women are more prone to hypothyroidism while taking lithium. This is not indicative of toxicity. Iodine uptake by the thyroid gland is impaired by lithium and therefore a decreased synthesis of thyroxine and compensatory increase in thyroid-stimulating hormone is the usual outcome. It is therefore good practice to determine thyroid function tests at least every 6 months. The thyroid-stimulating hormone level is increased in about 25% of patients and clinical hypothyroidism occurs in 10–20%. Goitre is less frequent, occurring in 5% of patients as a rule.

Prevention

In short, a physician should be on the alert for signs of side effects or toxic effects (e.g. fine tremor *vs* coarse tremor) when assessing a patient who has been prescribed lithium. Serum creatinine and thyroid function tests should be measured every 6 months (more frequently when patients are initially commenced on lithium), and a serum lithium level taken every 3 months at least. Some authors recommend testing for tubular and glomerular functions every 5 years (Alexander et al, 2008). Advice should be given to patients about potential changes in serum lithium levels when other drugs are used (*Table 2*). Commonly used drugs, for example, non-steroidal anti-inflammatory drugs, can raise lithium levels by 40%, angiotensin-converting enzyme inhibitors decrease excretion of lithium, and diuretics (especially thiazides) raise serum levels by reducing renal clearance. In general, therapeutic doses of thiazide diuretics result in a 25–40% decrease in lithium clearance with a concomitant increase in serum lithium levels. The nature of this interaction is quite variable and the most conservative approach is simply to avoid the use of thiazide diuretics if possible.

The widespread availability of herbal products on the Internet has also increased the potential for poisonings (Dunne, 2009). Older patients with decreased glomerular filtration rate are at greater risk of renal insufficiency after diuretic-induced volume contraction, and it is likely that patients treated long term with lithium are at higher risk of toxicity because of tubular damage and impaired sodium reabsorption.

The observation that patients newly treated with loop diuretics also have increased risk much higher than that associated with recent thiazides deserves other explanations. Indeed, in older persons, the use of loop diuretics or angiotensin-converting enzyme inhibitors may increase the risk of hospital admission for lithium toxicity, especially during the initial month of treatment (Laville, 2005). The loop diuretic furosemide increases lithium clearance by blocking reabsorption in the ascending limb of Henle, and thiazides act by blocking distal reabsorption. The increased amount of lithium arriving in the distal tubule induces a compensatory distal reabsorption that limits net excretion changes. Furosemide is a potent stimulator of the renin–angiotensin system and this in turn increases proximal lithium reabsorption. Furthermore, the increased sodium excretion induced by furosemide causes hypovolaemia and subsequent elevated lithium levels. Lithium primarily targets the distal and collecting tubules, with a higher incidence of proteinuria and associated glomerular pathology than recognized previously. Renal dysfunction is often irreversible despite lithium withdrawal, and early detection is essential to prevent progression to end-stage renal disease.

As a pharmacologically active cation, lithium is not metabolized in the body, but is excreted by the kidneys. Because it is a monovalent cation and does not bind to charcoal, the use of activated charcoal has no role in the treatment of lithium toxicity. Intravenous fluids may help restore urinary output and enhance real clearance. However, for patients with serious toxicity, haemodialysis or, if haemodialysis is not available, peritoneal dialysis (less effective) may be used to lower serum lithium levels. Long-duration haemodialysis for 12–16 hours will avoid a rebound effect as a result of the slow movement of lithium between intracellular and extracellular compartments. The usual cause of death in cases of acute overdose is pneumonia or shock. With appropriate attention to cardiac, renal and pulmonary function, and to the maintenance of fluid and electrolyte balance, most patients make a good recovery.

Continued absorption from the gut may be prevented by gastric lavage or whole bowel irrigation with poly-

Table 2. Drug interactions with lithium

Increased serum lithium levels	Thiazides
	Tetracyclines
	Metronidazole
	Non-steroidal anti-inflammatory drugs
	Angiotensin-converting enzyme inhibitors
	Angiotensin 2 antagonists.
Decreased serum lithium levels	Bronchodilators
	Verapamil
	Carbonic anhydrase inhibitors
	Antacids
Other potentially serious interactions	Ventricular arrhythmias with amiodarone
	Increased serotonergic effects with antidepressants
	Potential neurotoxicity with methyldopa, carbamazepine, haloperidol or phenytoin

ethylene glycol, although these procedures are controversial, and advice should be sought from a nephrologist. Because lithium has a low molecular weight and does not bind to protein, thereby making it readily dialysible, haemodialysis is generally preferred. In general, dialysis should be considered in patients with chronic toxicity and serum lithium concentrations higher than 3 mEq/litre, and in unstable chronic patients with lithium levels higher than 2.5 mEq/litre.

Conclusions

Lithium salts have been used in the prophylaxis and treatment of depression and bipolar disorder for some 60 years. Lithium has a narrow therapeutic range, and several well-characterized adverse effects limit the potential usefulness of higher doses. Furthermore, toxic symptoms do not always correlate with serum levels. An acute overdose in patients who have never used lithium is generally associated with a good prognosis because of extensive distribution of lithium throughout the total body water compartment. Conversely, prolonged use of lithium or an increase in dosage in patients already using the drug are associated with higher tissue concentrations because of the greater duration of exposure and therefore more serious consequences. Lithium toxicity may result in persistent cognitive and neurological impairment and, rarely, death. Therefore, in order to minimize exposure to high tissue concentrations, enhanced lithium clearance has been used.

KEY POINTS

- Lithium salts have been used in the treatment of bipolar disorder for over 60 years.
- Lithium has a narrow therapeutic range and therefore serum levels should be taken at least every 3 months.
- Serum lithium levels are best determined 12 hours after the last dose.
- Side effects are common and sometimes troublesome, particularly weight gain.
- Toxicity may occur despite a normal serum lithium level.
- Haemodialysis is usually effective in removing circulating lithium.

Haemodialysis is highly effective in removing circulating lithium, yet serum concentrations often rebound, and so repeated or prolonged treatment is sometimes necessary. With severe lithium poisoning haemodialysis may aggravate haemodynamic instability. Therefore, continuous renal replacement therapy has been advocated (van Bommel et al, 2000) because it allows slow and continuous solute removal. Continuous arteriovenous haemodiafiltration and continuous venovenous haemodiafiltration increase lithium clearance, albeit to a lesser extent than haemodialysis, and are more widely accessible. Rebound effects are offset when haemodiafiltration is sustained for longer than 16 hours as it allows effective removal of total body lithium (Waring, 2006). The choice between the different treatment techniques will depend on local availability and the patient's condition, and should be determined by consultation between anaesthetists and renal physicians. **BJHM**

Conflict of interest: none.

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