

Lithium: mimicry, mania, and muscle relaxants



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Key points

Lithium is an alkali metal used in the management of bipolar disorder.

Lithium mimics sodium in excitable tissues.

A narrow therapeutic window and long half-life make toxicity a risk.

Severe toxicity is an indication for haemodialysis.

Lithium potentiates the action of neuromuscular blocking agents.

Lithium is an alkali metal, found in Group 1 (Period 2) of the Periodic Table. It is represented by the letters 'Li' and has an atomic number of 3. It is the least dense of all the metals; having a metallic silvery surface when cut, which quickly tarnishes to grey in the presence of oxygen (Figs 1 and 2). It tends to lose an electron to form Li^+ . Lithium is highly flammable and burns with a crimson flame. It is commonly found in light-weight alloys, batteries, and lubricants. Lithium is normally ingested by living organisms from dietary sources. It is present in trace amounts in the human body.

Role in medicine

In the nineteenth century, lithium was known to combine with uric acid to produce a soluble salt and was used as a treatment for gout, rheumatism, and renal stones. John Cade (1912–80), an Australian psychiatrist, is credited with discovering lithium's mood-stabilizing properties.¹ Cade hypothesized that mania was caused by a normal waste product of the body circulating in excess. He believed urea to be the toxic substance responsible and used lithium urate to investigate the psychiatric effects of urea toxicity. Cade found that guinea pigs injected with lithium urate became placid, lethargic, and less responsive to external stimuli. He subsequently found lithium rather than urea to be the active component and went on to demonstrate a therapeutic effect in human patients with mania. Modern indications for lithium, usually given as lithium carbonate are:^{2, 3}

1. acute treatment of mania and hypomania;
2. prophylaxis of chronic bipolar depression;
3. prophylaxis of recurrent depression;
4. prophylaxis of chronic cluster headache.

Lithium has also been considered useful in the management of neuropathic pain, central pain, and phantom tooth pain. The metal has a very narrow therapeutic window being clinically effective at 0.5–1.0 mmol litre⁻¹ but toxic over 1.5 mmol litre⁻¹.¹ Facilities for

measuring plasma levels are a prerequisite to prescribing.

Mechanism of action

The mechanism by which lithium has its therapeutic effect is complex and not fully elucidated. It is known to increase the uptake of norepinephrine by the presynaptic membrane and increase its subsequent metabolism by monoamine oxidases.³ This may counter the increase in catecholamines believed to occur in mania. Second messenger systems may be another target, lithium can inhibit adenylate cyclase—reducing cAMP signalling. Nahorski and colleagues⁴ suggested interference with the phosphatidylinositol second messenger pathway.

Pharmacokinetics

Lithium is rapidly absorbed after oral administration and has 100% bioavailability.⁵ Peak plasma levels usually occur 1–4 h after a single dose. Volume of distribution approximates to total body water.³ Lithium is not bound to plasma proteins. It tends to accumulate in bone and thyroid tissue.

Lithium is excreted via the kidneys and exhibits rapid and delayed phases of excretion.¹ Approximately half of an oral dose is excreted within 12 h of administration. The remainder takes 7–14 days to be eliminated. The ion is freely filtered at the glomerulus following which 80% is reabsorbed via the proximal tubule.³ The proximal tubule is the only site of lithium reabsorption in the kidney and the process is competitive with sodium reabsorption.³

Side-effects: dose-independent effects

Lithium is well recognized to disrupt thyroid hormone homeostasis and may cause goitre formation, hypothyroidism, or both. It is also a cause of nephrogenic diabetes insipidus, commonly presenting as polyuria and polydipsia.⁶ Both of these effects are

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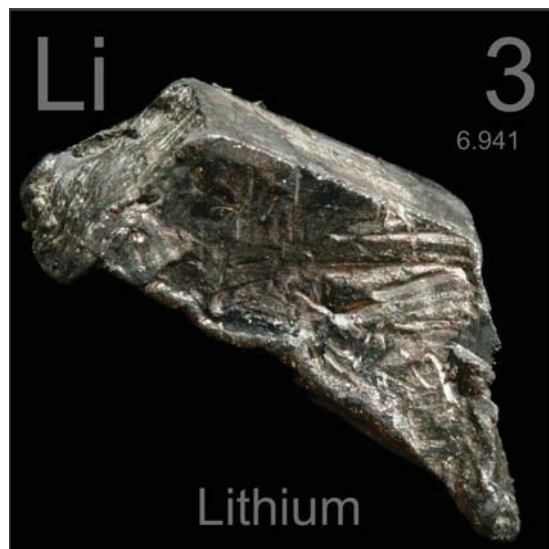


Fig 1 Lithium is the lightest of all metals, is soft enough to cut by hand, and has a shiny metallic surface. ©Theodore Gray 2009. Reproduced with permission.

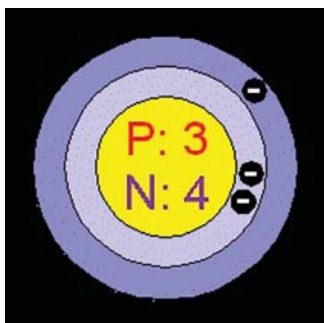


Fig 2 A schematic diagram of lithium's atomic structure. Figure reproduced with permission from Professor Duncan Double, University of East Anglia.

thought to be due to interruption of the cAMP second messenger system.³

Chronic administration of lithium may cause weight gain, pretibial oedema, and occasionally extra-pyramidal effects.^{1, 5} Lithium effects on the electrocardiogram include T wave flattening/inversion and QRS widening.³ It may mimic the changes of hypokalaemia. Lithium can disrupt normal cardiac conduction pathways and cause sinoatrial block or atrioventricular block. Myocarditis has been reported.³

Toxicity

The combination of a narrow therapeutic window and long plasma half-life (8–48 h) mean toxicity is a real clinical risk and monitoring of plasma levels is essential. Peak plasma levels may occur as early as 30 min after oral liquid preparations but may be delayed by as long as 5–6 h after sustained release tablets.⁷ Symptoms and signs of toxicity are listed in **Box 1**.

Box 1 Signs and symptoms of lithium toxicity

- Nausea and vomiting
- Abdominal pain
- Diarrhoea
- Blurred vision
- Ataxia and tremor
- Dysrhythmia
- Nystagmus
- Hyper-reflexia
- Convulsions
- Coma
- Death (>3 mmol litre⁻¹)

These hyperexcitable toxic effects are thought to be due to lithium mimicking another monovalent cation in the body: sodium. Lithium, by mimicking sodium, is able to permeate the fast voltage-sensitive channels present in excitable tissues responsible for action potential generation. However, unlike sodium, it is not effectively removed from the intracellular compartment by Na/K ATPase and tends to accumulate. High intracellular concentrations of lithium displace potassium, leading to partial depolarization of the membrane.¹ Risk factors⁷ for toxicity include change of dosing regimen, acute renal failure, and hyponatraemia. Plasma levels may increase when lithium is coadministered with diuretics, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, and metronidazole. There is an increased risk of neurotoxicity without change in plasma level when prescribed with venlafaxine, carbamazepine, phenytoin, haloperidol, verapamil, and methyl dopa. Plasma levels are lowered by acetazolamide and theophylline via increased renal excretion.⁷

Management of toxicity

Patients with a single acute overdose may show only mild signs of toxicity. However, even a small acute overdose on a background of chronic lithium use may prove life threatening as body tissues are already saturated. Other risk factors for serious toxicity include hypertension, diabetes, congestive heart failure, chronic renal failure, and Addison's disease.⁷

Initial management should ensure airway patency and adequacy of ventilation, especially in a patient with impaired consciousness. ECG monitoring is recommended. Plasma levels should be taken immediately, 6 h, and then every 6–12 h (in non-lithium-heparin blood tubes!). If presentation is within 1 h of ingestion, consider gastric lavage in adults who have taken >4 g, ensure adequate hydration, and correct any electrolyte imbalance. Forced diuresis and thiazide diuretics are contraindicated. Benzodiazepines should be used to manage seizures. Haemodialysis is the definitive treatment for severe poisoning (**Box 2**).⁷ Clinical improvement may lag behind a decrease in plasma lithium levels. Blood lithium levels may increase significantly on stopping haemodialysis.

Box 2 Indications for haemodialysis in lithium toxicity

1. Neurological symptoms or signs
2. Plasma lithium >7.5 mmol litre⁻¹ in acute overdose
3. Plasma lithium >4.0 mmol litre⁻¹ in acute on chronic overdose

Lithium and anaesthesia

Lithium administration prolongs both depolarizing and non-depolarizing neuromuscular block.^{5, 8} Its action appears to be synergistic with non-depolarizing neuromuscular blocking agents and additive with depolarizing neuromuscular blocking agents. Potentiation of neuromuscular block by lithium has occurred after succinylcholine and pancuronium administration.⁸ It is likely to be true for the other non-depolarizing neuromuscular blocking agents. All patients on lithium undergoing general anaesthesia with the use of neuromuscular blocking agents should receive appropriate neuromuscular monitoring.

Case reports have described a prolonged hypnotic effect in barbiturate-based anaesthesia in patients who are taking lithium, although in one report the plasma lithium level was above the normal therapeutic range.⁹ The effects of lithium on other classes of induction agent have not been studied. It is suggested that lithium be omitted in the 24 h preceding general anaesthesia.⁹

Lithium has been associated with conduction defects and ST changes on ECG under anaesthesia. Although in one such case report, maintenance of anaesthesia was somewhat dissimilar to current practice: 66% nitrous oxide in oxygen with boluses of fentanyl and pancuronium.¹⁰

Lithium and pregnancy

Lithium therapy may impact on both mother and fetus. The normal physiological changes of pregnancy may alter a previously stable plasma lithium level. The increase in extracellular fluid volume during pregnancy may lead to an increase in volume of distribution and a decrease in plasma concentration.⁸ A higher glomerular filtration rate (GFR) will increase lithium clearance and also lower plasma levels. Hyperemesis gravidarum in early pregnancy or poor oral intake during labour will tend to cause an increase in plasma levels.⁸ Pre-eclampsia is often associated with acute renal impairment and risks precipitating lithium toxicity. A further cause of acute kidney injury in pregnancy is mechanical ureteric obstruction from the gravid uterus.⁸ It is estimated that 90% of women develop asymptomatic unilateral upper urinary tract obstruction in the final trimester of pregnancy.⁸ In eight out of 10 cases, this is right-sided, the left ureter being partially protected by the overlying sigmoid colon. Symptomatic lithium toxicity in a 39-yr-old female with twins at 34 weeks secondary to ureteric obstruction has been reported in the literature.⁸

Lithium can cross the placenta and is well recognized to cause fetal morbidity. First-trimester exposure is teratogenic, causing a three-fold increase in the incidence of all congenital malformations and an eight-fold increase in cardiac abnormalities such as Ebstein's anomaly (prolapse of the tricuspid valve into the right ventricle).⁸ Babies born to mothers taking lithium have significantly lower Apgar scores, longer hospital stays, and higher rates of neuromuscular complications. Lithium can contaminate breast milk and its administration is therefore a relative contraindication to breast feeding.⁸

Guidelines have been published regarding the use of lithium therapy in pregnancy. If possible, lithium should be stopped before conception. There are, however, significant risks to mother and fetus from uncontrolled bipolar disorder. The Confidential Enquiry into Maternal Death 2000–2 identified suicide as the most common overall cause of maternal death. There is also a morbidity burden from self-harm, alcohol excess, and abuse of other substances that may result from poorly controlled psychiatric illness. Each patient should therefore have their treatment planned by the multidisciplinary team according to their individual risks. If possible, lithium should be stopped 24–48 h before delivery to minimize plasma concentration in the fetus. Maternal lithium levels should be monitored and women kept well hydrated during labour and delivery.⁸

Role in clinical measurement

Lithium dilution is an established method of cardiac output monitoring. It is comparable with indocyanine green dye dilution or thermodilution via a pulmonary artery flotation catheter. A bolus of lithium (0.075–0.3 mmol) is injected i.v. and a lithium dilution curve is generated from an ion-selective electrode incorporated into a peripheral arterial cannula. Cardiac output may be derived from the area under the dilution curve. This small dose of lithium has no known pharmacological effects. Lithium has several advantages over previously used indicators. Thermodilution has a low signal-to-noise ratio and loses signal quality quickly. This necessitates central venous access for injection and centrally placed invasive monitoring devices for detection; exposing the patient to all the associated risks of a pulmonary artery flotation catheter. Lithium by comparison has a high signal-to-noise ratio, allowing the signal to travel greater distances and be detected peripherally using less invasive lines. Studies have shown the peripheral venous route to be as effective as central venous injection; the technique may therefore be used in patients without a central venous catheter. Indocyanine green is not easily re-distributed and is unsuitable for conducting multiple measurements in a short period of time. Lithium is re-distributed in 3–5 min and can therefore be used for frequent repeat measurements of cardiac output. LiDCO[®] monitors are currently priced at £17 318 with disposables costing approximately £100 per patient. Lithium chloride itself costs £18 per 10 ml ampoule, with 2 ml being a standard bolus dose. Lithium dilution cardiac output monitoring is unsuitable for patients on chronic lithium therapy as detecting a tiny bolus dose against the background plasma level would be equivalent to looking for a needle in

a haystack. Other contraindications include patients weighing <40 kg and women in the first trimester of pregnancy.

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© Theodore Gray 2009. Hannah Paterson, Sales Executive, LiDCO Ltd, for providing information on LiDCO®. Professor Duncan Double, University of East Anglia, for permission to use Figure 2.

Conflict of interest

None declared.

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Please see multiple choice questions 7–10