

This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Lithium

Lithium is a drug used to treat severe mental disorders. The usual clinical indications are:

- Treatment of acute mania
- Maintenance prophylactic treatment in bipolar affective disorder
- Treatment of severe or treatment-resistant depression (to augment high dose antidepressants)

In the general hospital setting the vast majority of encounters with lithium involve patients already taking it prior to admission. Commencing a patient on lithium requires specialist psychiatric input. If a patient is to be commenced on lithium whilst an inpatient this must be overseen by a consultant psychiatrist in the Psychological Medicine Service.

Serum levels of lithium are sensitive to changes in the body caused by physical illnesses and drug interactions. The management priority is to minimise risks of lithium toxicity or sub-optimal treatment. Therefore, it is essential for clinicians to ensure lithium is prescribed safely and is appropriately monitored during a patient's admission to hospital.

Pharmacology of lithium

Lithium is in the same group of the periodic table as sodium and the body does not distinguish between these cations. Lithium kinetics therefore follow those of sodium. This underlies how lithium toxicity arises. Essentially, sodium depletion of any cause can lead to lithium toxicity as the kidney actively retains lithium in place of sodium.

Lithium levels

The **target therapeutic serum level is 0.4 – 1mmol/litre**. (Note that an individual patient may have

a more precise target range, depending on their diagnosis and drug response.)

The dose (usually nocte administration) can range widely between patients, from 200mg to above 1g; however much is required to achieve therapeutic serum levels.

Lithium is usually administered as a single nocte dose but can also be administered on a twice-daily regimen.

Lithium toxicity can arise from serum levels of 1.1mmol/l upwards. Clinical severity is dose-related but is determined primarily by the patient's degree and number of symptoms rather than the serum concentration alone. Toxicity may constitute a medical emergency

Monitoring lithium levels

A valid lithium level is obtained 12 hours after the last dose.

Routine measurements for patients in the community are conducted every 3-6 months. The NPSA Alert states that lithium levels should be every three months, kidney and thyroid checks every 6 months and full health check every 12 months¹.

in addition to baseline monitoring It is essential to ensure monitoring is performed whenever the patient's clinical status changes, especially in the context of acute medical illness or when interacting medication is started or stopped.

Patients receiving lithium who are admitted to hospital acutely unwell must have their lithium level measured at the earliest opportunity to obtain a 12 hour post-dose level.

Over the course of the admission levels will need to be monitored closely; the precise frequency should be determined by the clinical circumstances. Patients taking lithium should have a lithium record book. Any changes to doses and any levels monitored should be documented in the book whilst in the hospital

Risk factors for lithium toxicity

- Acute medical illness
- Renal disease
- Dehydration (important to be aware of this in hot weather)
- Drug interactions

Adverse effects of lithium^{2,3}

It is essential to distinguish side effects of lithium from features of lithium toxicity.

Side effects

Short-term:

- Gastrointestinal disturbance
- Metallic taste
- Fine tremor
- Polyuria and polydipsia

Longer-term use:

- Renal impairment
- Nephrogenic diabetes insipidus
- Hyperparathyroidism
- Thyroid dysfunction
- Weight gain
- Mild cognitive impairment

Toxicity²

These symptoms present on a spectrum of mild to severe, and may constitute a medical emergency.

- **Haemodynamic changes** including dehydration, acute kidney injury, hypotension
- **GI disturbance** including anorexia, severe (possibly bloody) diarrhoea
- **CNS effects** including confusion, ataxia, dysarthria, weakness, hypertonia, drowsiness, coarse tremor, seizures, coma. If not managed urgently neurological toxicity may not be reversible.

Management of lithium toxicity

- Aim for supportive treatment to correct fluid and electrolyte imbalance, and renal dysfunction
- Withhold lithium
- Discuss with Psychological Medicine about alternative management of mental disorder
- Senior medical input essential and discussion with renal physicians may be necessary
- Rehydration with IV fluids
- Monitor fluid input and output
- Close monitoring of renal function, glucose and lithium levels
- Severe toxicity may require haemodialysis

Drug interactions^{2,3}

Drugs that affect sodium kinetics can cause lithium toxicity, so should not be co-prescribed without senior supervision and frequent monitoring. It is important to note that some of these drugs can be purchased by patients as over-the-counter medications.

ACE Inhibitors and Angiotensin II antagonists²

ACEIs especially can cause mild dehydration and increase sodium excretion at the renal glomerulus. Sodium, and therefore lithium, are reabsorbed by the kidney.

The effect is not acute, and can take a number of weeks to develop. The risk is especially increased in the elderly.

Diuretics²

These drugs reduce lithium clearance. Thiazide diuretics have a greater effect than loop diuretics. The effect is much quicker than with ACEIs; levels can rise within 10 days.

NSAIDs and COX-2 inhibitors²

These drugs reduce renal blood flow by inhibiting production of renal prostaglandins. They may also increase renal cation reabsorption. The effect on lithium levels can arise within a few days.

It is important to ensure patients are aware of this interaction due to the availability of NSAIDs over the counter.

Metronidazole

May cause increased lithium levels.

Theophylline

May cause increased lithium excretion and reduced serum levels.

Haloperidol and carbamazepine

These drugs do not affect lithium metabolism but can cause neurotoxicity when co-prescribed with lithium. This is important to bear in mind in patients presenting with delirium or acute behavioural disturbance.

Sodium

Sodium-containing antacids, alkalising medicines and bicarbonate, should not be used. As discussed earlier the kidney cannot distinguish between sodium and lithium. Therefore if a patient increases their oral sodium intake, for example in the form of an antacid the kidney will excrete the sodium not needed along with the lithium, reducing lithium levels. Conversely if the patient restricts dietary sodium then toxic lithium levels may be seen as the kidney reabsorbs both sodium and lithium⁴.

Lithium potentiates the effect of serotonergic drugs and hence may precipitate or contribute to the development of the serotonin syndrome. Features of the serotonin syndrome include: mental state changes, autonomic dysfunction and neuromuscular hyperactivity. It is important to know that symptoms of serotonin syndrome and lithium toxicity can overlap. Serum lithium levels will of course be crucial in obtaining a diagnosis, and thereby helping decide which drugs may need to be omitted. Senior or specialist support should be sought.

Stopping lithium

Lithium is not a drug of misuse or dependency and there is no known lithium withdrawal syndrome. However, abrupt withdrawal of lithium can precipitate relapse of a patient's mental illness.

Cessation of lithium therapy should be planned and weaned over a period of several weeks under supervision from a mental health team.

In the emergency situation with severe **lithium toxicity** it may be necessary to stop lithium immediately. In such situations it may also be necessary to commence another psychotropic in place of lithium to cover treatment of the patient's mental disorder. It is essential to consult with the Psychological Medicine Service over this decision.

In more equivocal situations of high but non-toxic levels the risk of lithium toxicity needs to be balanced against the risk of mental disorder relapse. In such situations it may be necessary to temporarily withhold lithium until serum levels normalise. Again, advice should be sought from the Psychological Medicine Service.

Lithium formulations

Lithium is available in two salts:

- Lithium carbonate, the most commonly prescribed salt, available in tablet form.
- Lithium citrate, for patients requiring liquid lithium.

Preparations of the two salts differ significantly in terms of bioavailability. The most commonly prescribed brands of lithium carbonate; Priadel and Camcolit, can also differ in their bioavailability as well.

It is essential therefore that when taking a drug history clinicians confirm the preparation and brand of lithium so that the patient can be continued on their usual drug regimen with minimal disruption to their serum levels.

If a patient becomes unable to swallow their regular tablets, contact pharmacy for advice on switching between tablets and liquids.

Lithium and surgery

Lithium does not interact with any of the main anaesthetic agents but there is a potential increased risk of arrhythmia.²

The main issue in surgery is the risk of toxicity precipitated by fluid loss or dehydration. For routine minor surgery, lithium should not routinely be withheld in the perioperative period. A 12 hour lithium level must be taken before and after surgery.

For elective major surgery, guidelines² recommend slow weaning ahead of surgery. This should be supervised by the GP or community mental health service. If this has not taken place it will be necessary to consult with the Psychological Medicine Service when the patient is admitted to hospital.

In emergency surgery it will not of course be possible to do this. The anaesthetist must of course be made aware of the prescription. The crucial aspect in this situation will be in post-operative management and minimising risks of toxicity.

Frequent post-operative monitoring may be necessary due to risks of dehydration, renal dysfunction and electrolyte imbalance.

If a patient is nil by mouth or unable to swallow tablets in the perioperative period, it may be necessary to switch to liquid lithium citrate. The bioavailability difference must be borne in mind and any switch must

be discussed with a pharmacist. If the patient cannot have enteral medication an alternative psychotropic may need to be prescribed to cover the enforced lithium holiday. The Psychological Medicine Service must be consulted on this decision.

SUMMARY

- Always check Lithium levels in acutely unwell patients
- On admission and during hospital stay, ensure regular electrolytes levels are taken, as hyponatraemia can affect lithium levels.
- Always prescribe Lithium as, lithium and with its brand name.

Medical teams should seek to consult with the Psychological Medicine Service for any advice on the management of lithium

References

1. Safer Lithium Therapy. Patient Safety Alert. NPSA/2009/PSA005 Dec 2009.
2. Taylor D, Paton C, Kapur S *The Maudsley Prescribing Guidelines in Psychiatry, 11th Edition* (2012) Wiley-Blackwell
3. British National Formulary 66 (2014)
4. Stockleys Drug Interactions via medicines complete

Author Dr Michael Yousif (Consultant Psychological Medicine)

With Contribution from Katharine Westcott (medicine Information Pharmacist) and Neha Shah (Governance Support Pharmacist)

Review date: January 2019