

# Lithium

## in General Practice

### Key Points

- The dose of lithium should be carefully individualised according to serum drug concentrations, therapeutic response and dose related toxicity.
- Baseline biochemical investigations and regular routine monitoring (including asking the patient about side effects) are essential for the early identification and management of adverse drug reactions.
- Many factors (compliance, drug interactions, diet, fluid intake, illness) can influence lithium concentrations and need to be considered when interpreting reports.
- As many adverse effects are dose related the lowest effective dose of lithium should be used. The therapeutic range for prophylaxis is between 0.6–0.8 mmol/L and in acute treatment is 0.8–1.2 mmol/L.
- If available, refer to the person's 'lithium history' of response and adverse effects for a guide to management.
- Optimal management of patients on lithium requires good communication between all health care providers.
- Patients and their relatives or carers should be well informed on the identification of early signs of toxicity and adverse effects.

### Introduction

Lithium remains a mainstay of treatment for bipolar disorder but dose individualisation, measurement of serum drug concentrations and monitoring for adverse reactions are vital in order to maximise therapeutic response. Lithium has a narrow therapeutic index and drug interactions, changes in diet and fluid intake, illness and compliance can all markedly affect serum drug concentrations reducing therapeutic response or causing toxicity. In most cases lithium will be started by a specialist but the GP has an important role to play to ensure optimal management.

**In this article we provide an overview and guidance on the management of patients taking lithium. We do not consider clinical indications in detail.**

### Indications for Lithium

Lithium is a mood stabiliser. In bipolar disorder it is indicated for acute hypomanic/manic episodes, acute bipolar depression and prophylaxis. Other effective mood stabilisers include sodium valproate, carbamazepine, atypical antipsychotics, and lamotrigine (in bipolar depression). The principles for the use of lithium in bipolar disorder are described in a recent RANZCP guideline.<sup>1</sup>

**Expert Review:** Professor Pete Ellis - Wellington School of Medicine and Amanda Wheeler, Specialist Pharmacist - Waitemata DHB.

## **Acute manic episodes**

Lithium is used as a mood stabiliser with or without adjunctive/symptomatic treatments such as an antipsychotic or benzodiazepine to manage sleep, agitation, psychosis or aggressive behaviour.

## **Acute bipolar depression**

Lithium is recommended as first-line treatment unless in the past it has been unsuccessful. It may be used as a mood stabiliser with or without an antidepressant. Concomitant antidepressant use is recommended when a faster onset of antidepressant action is required as the antidepressant effects of mood stabiliser monotherapy may take four to six weeks to develop.

## **Prophylaxis of bipolar disorder**

Lithium is used at a lower dose for prophylaxis of bipolar disorder when acute episodes have resolved.

## **Other**

Lithium is also used for augmentation of antidepressant treatment in patients with treatment resistant depression. Whilst it is not registered for this use in New Zealand there is evidence of its benefit when there has been unsatisfactory response to antidepressant treatment. Local guidelines for the treatment of depression recommend lithium augmentation as a possible strategy in this treatment resistant patient group.<sup>2</sup>

## Formulations of lithium

Lithium is available in New Zealand as lithium carbonate. There are three different forms of lithium available:

- Lithium Carbonate 250 mg capsules (Douglas brand).
- Lithium Carbonate 250 mg and 400 mg film coated tablets (Lithicarb).
- Lithium Carbonate 400 mg slow release tablets (Priadel).

These forms have different bioavailability and different release profiles. For this reason these are not interchangeable. When prescribing lithium it is important that you specify which brand or form is to be dispensed.

If it is necessary to change brands of lithium, additional lithium serum level monitoring should be instituted, until the level has stabilised. The level should be measured five days after the change, then weekly until restabilised at the desired serum level.

**Dose adjustment example:** A person's serum concentration is 1.0 mmol/L after a week of reliable dosing on a daily dose of 800 mg lithium carbonate. A reduction in dose to 600 mg should give a new steady state concentration of 0.75 mmol/L. This should be checked at least five days after the dose reduction.

## Dosage and administration

Initiation is usually by a specialist and the patient will normally be stabilised by the time they reach care in general practice. The GP has a vital role in maintenance of optimal treatment and identifying the need for dosage adjustment. The daily dose is individualised according to therapeutic response and serum drug concentrations but is usually in the range 400 – 1200 mg daily. Lithium may be given as a single daily dose in the morning or at bedtime. Alternatively, the dose may be divided and given morning and evening, however polyuria can occur more frequently with twice daily dosing. Once-daily dosing may reduce the risk of renal damage and adverse effects and simplifies the dosing regimen.<sup>3,4</sup> For these reasons once-daily dosing, may be preferred.

## Dosage adjustment

Lithium exhibits linear pharmacokinetics, which means that the steady state serum concentration is proportional to the dose, therefore doubling the dose will double the concentration and vice-versa (see example below).

## Adverse effects of lithium

Adverse effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 mmol/L. Mild gastrointestinal effects (mild nausea, vomiting and diarrhoea), vertigo, muscle weakness and a dazed feeling may occur initially, but frequently disappear after stabilisation. Fine hand tremors, polyuria and polydipsia (mild thirst) may persist. Mild polyuria may not be of concern but may be troublesome and the possibility of diabetes insipidus should be considered.

Skin conditions including acne, psoriasis, generalised pustular psoriasis, rashes and leg ulcers can be aggravated by lithium treatment.

Lithium has several less common but important metabolic adverse effects. Prevention and avoidance of risk factors are important keys to management (Table 1). Patients and their families/carers should be educated about early warning signs of all adverse effects, and the need for immediate advice if clinical signs of lithium toxicity such as severe or persistent diarrhoea, vomiting, tremor, mild ataxia, drowsiness or muscular weakness occur.

**Table 1 Metabolic adverse effects of lithium**

<p><b>Thyroid disorders</b></p>	<p>Hypothyroidism is common and is seen more frequently in women than men.<sup>5</sup>          Biochemical changes identical to those in primary hypothyroidism.          Risk factors include elevated thyroid autoantibodies or TSH at baseline, family history, middle age, high lithium concentrations.          Overt hypothyroidism is treated with thyroxine replacement. Management of subclinical hypothyroidism may be beneficial.          Hyperthyroidism reported but relatively rare.</p>
<p><b>Weight gain</b></p>	<p>Significant weight gain is common and may lead to reduced compliance.<sup>6</sup>          Reported risk factors include high baseline weight, young age, female gender and concurrent antidepressants. The mechanism may involve increased intake of high calorie drinks to relieve thirst.          Weight gain or oedema should not be treated with diuretics.          Management includes counseling and dietary management. In severe cases other agents such as valproate or carbamazepine may be considered but they can also cause weight gain.</p>
<p><b>Nephrogenic diabetes insipidus</b></p>	<p>Lithium is the most common drug cause, affecting 10% of patients treated for 15 years or more.<sup>7</sup>          Risk correlates with duration of lithium treatment.          Presents as polydipsia and polyuria (24 hour urine volume &gt; 3 L).          Dehydration, lithium intoxication and deteriorating renal function may occur and renal impairment may be permanent.          Risk factors include long term treatment, concurrent use of long term NSAIDs, chronic physical illness and increasing age.          Avoidance includes careful monitoring and awareness of risk factors. Management may include shared care with renal specialist and switch to alternative treatment.</p>
<p><b>Hyperparathyroidism</b></p>	<p>Hypercalcaemia is common. Reported incidence as high as 50%. More common in women and elderly. Not linked to lithium concentrations, treatment duration or cumulative dose. May lead to renal stones, worsening psychiatric condition, dehydration and renal impairment.<sup>6</sup>          If Hypercalcaemia is mild (corrected Ca &lt; 2.75 mmol/L) adopt a conservative approach. If clinical manifestations are present changing to another drug may be necessary.          Corrected calcium levels above 2.75 mmol/L would usually warrant discussion with a renal physician.</p>

## Avoid lithium in pregnancy

Avoid the use of lithium during pregnancy whenever possible. The overall risk of foetal malformations is 4–12% in the first trimester and therefore greater than the general population. Cardiovascular malformations include Ebstein's anomaly, which can be detected by foetal echocardiography at 16–18 weeks gestation. Specialist review of the use of lithium (and all other mood stabilising drugs, including lamotrigine) is indicated in any woman considering becoming pregnant, and all those who have become pregnant before discontinuing mood stabilisers. The relative risk to the mother of discontinuing treatment needs to be balanced with the risks to the foetus.

## Pharmacokinetics and serum concentrations

Lithium is excreted unchanged and partially reabsorbed by the kidney. The half-life is approximately 24 hours (longer in renal impairment) which means that steady state drug concentrations are reached four to five days after initiation or a change in dose. Changes in renal function, fluid and electrolyte balance and interacting drugs can alter drug concentrations as can irregular dosing, poor compliance and missed doses. These factors need to be considered as an explanation for poor therapeutic response or toxicity.

### Serum Level Monitoring

Lithium serum levels should be taken **10-14 hours post-dose**.

Lithium serum levels should be measured:

- if there are signs of lithium toxicity (see opposite page)
- five days after initiation or change in dose, change in brand, change in dosage regimen (e.g. twice daily to once daily) or change to potentially interacting medication
- weekly during acute treatment
- every three months once patient's mental state and lithium serum level are stable

### Therapeutic range

For acute episodes a concentration towards the upper end of the range may be required (0.8–1.2 mmol/L). Some evidence suggests that the minimum therapeutic serum lithium level for acute mania is around 1.0 mmol/L. When a patient is acutely manic, lower serum levels may be seen than when the patient is euthymic despite the same dose of lithium. If the lithium dose is increased to treat the acute episode, it is essential to monitor the patient for clinical signs of toxicity. Repeat the lithium serum levels at least weekly as the episode resolves as the patient's lithium serum level may rise.

Once the acute episode is resolved the lithium dose can usually be adjusted downwards to achieve a maintenance lithium serum level of between 0.6–0.8 mmol/L.<sup>1</sup> Serum levels lower than this are only warranted if the patient has had unacceptable adverse effects or has a history of maintenance of lower serum levels without relapse.

## Signs of lithium toxicity

Toxicity generally occurs at concentrations > 1.5–2.0 mmol/L, but may do so at concentrations within the therapeutic range, especially in elderly people. Concentrations > 3.5 mmol/L are potentially fatal and haemodialysis is recommended.<sup>1</sup>

Signs of lithium toxicity include; blurred vision, GI disturbances (increasing anorexia, nausea, vomiting and diarrhoea), muscle weakness, coarse tremor, lack of co-ordination, ataxia, dysarthria, drowsiness, sluggishness, confusion and convulsions.

**Development of any of these signs necessitates an urgent lithium serum level. This should still be done 10–14 hours after the last dose, however the next dose should be withheld until the lithium serum level has been checked and the dosage adjusted as necessary.**

## Interpretation of serum lithium concentrations

The therapeutic range is simply a guide and there will be occasional patients who are controlled on concentrations outside the accepted range. It is important to assess individual patient response and signs of toxicity in conjunction with the serum concentration. A person on long term lithium may have an individual 'lithium history' indicating the serum concentrations normally associated with clinical response or dose related side effects for that individual.

The sampling time should be standardised at 10–14 hours after the last dose and should be consistent for each person. Interpretation is unreliable if sampling times are variable. If it is uncertain if a patient is compliant, reinforce the need for this and re-check the concentration after five days to ensure a reliable steady state result.

## Reasons for changes in measured serum lithium concentrations

- Variation in sampling time. For example, a sample is taken at 18 hours post dose but is usually measured at 12 hours.
- Change in dose regimen. For example, if the dose is switched from once daily to twice daily the 12 hour post dose concentration will be lower.
- Compliance issues. Poor compliance is common as patients have a tendency to stop taking lithium if they feel well, or to reduce adverse effects such as tremor.
- Renal function
  - A decrease will raise lithium concentrations.
  - An increase reduces lithium concentrations
- Interacting drugs; NSAIDs, ACE inhibitors and diuretics may raise concentrations and the risk of toxicity may be exacerbated with dehydration, vomiting and diarrhoea, and change in salt/fluid balance. Theophylline may decrease concentrations.
- Dehydration, GI upset (vomiting and diarrhoea), or change in salt or fluid balance may alter lithium concentrations and increase the risk of drug interactions.
- Crash diets, change to vegetarian diet (with much lower sodium content) and physical illness are often associated with increases.
- Brand changes. Different brands and dose forms (slow release vs normal release) have variable bioavailability. Always prescribe the same brand and formulation of lithium.

# Interpretation of serum lithium concentrations

## Interpretation and action (Adapted from Lothian Guidelines)<sup>8</sup>

### ***The concentration is low (e.g. < 0.6 mmol/L)***

- If the person is well and the concentration is consistently low, but the norm for that individual, a dose alteration is not required.
- If the patient is unwell and a series of concentrations have been bordering on the lower end of the range:
  - Assess compliance
  - Re-check concentration after five days
  - Increase dose if appropriate

### ***If the concentration is within the therapeutic range (e.g. 0.6–0.8 mmol/L)***

- If the person is well and tolerating no action is required.
- If the person is well but complains of dose related side effects:
  - Investigate and exclude possible reasons for increased lithium concentrations, especially if these are higher than the norm for the individual.
  - If appropriate try a small dose reduction with assessment of clinical response.
- If the person is unwell increase the dose to within the acute treatment range (0.8–1.2 mmol/L). Liaise with a specialist if there is no response or adverse effects develop.

### ***If the concentration is high (typically > 1.0 mmol/L), but with no signs of toxicity)***

- Investigate possible explanations for high concentration. Correct where possible and re-check the concentration.
- If the concentration is one of several which have bordered on being too high, encourage fluids, re-check level after five days and consider a dose decrease.
- If there is no clear explanation for the high concentration; re-check and investigate renal function.
- N.B. Some people may need a relatively high concentration for control. Does the 'lithium history' indicate a reduced response if concentrations are lower? Extra vigilance for toxicity is required.

## Baseline tests and monitoring

Recommended baseline tests and ongoing monitoring are described in Table 2. There may be slight local variations in these guidelines. As well as biochemical monitoring it is important to look for and educate patients about physical signs and symptoms associated with adverse effects and toxicity. These include tremor, tiredness, lethargy, nausea, vomiting and diarrhoea, dehydration, polydipsia, polyuria and nocturia. Although baseline tests will be carried out when lithium is initiated by a specialist, check that the results are complete and readily available for reference.

**Table 2 Lithium baseline tests and monitoring.<sup>6,9</sup> (adapted from Livingstone, 2006; Waitemata DHB 2006)**

	<b>Baseline</b>	<b>Routine maintenance</b>	<b>Comments</b>
<b>Serum lithium concentrations</b>	Important to establish reliable steady state concentration associated with therapeutic response	3-monthly	Monitor more frequently in high risk patients, e.g. those on potentially interacting drugs, poor compliance, elderly, unstable renal function, physical illness
<b>Thyroid Function</b>	Baseline thyroid function (T4, TSH)	TSH 3 months after initiation and then 6-monthly	T4 not routinely required. Monitor for symptoms of hypothyroidism
<b>Electrolytes</b>	Baseline	Check with lithium serum levels every 3 months	Particularly important to monitor sodium as it competes for reabsorption in proximal renal tubule
<b>Serum creatinine and renal function</b>	Exclude renal disease. Baseline creatinine and estimation of renal function	Check at same time as lithium levels, at least every 3 months	Estimate renal function using the Cockcroft and Gault Equation* based on ideal body weight
<b>Serum calcium and magnesium</b>	Baseline	Check every 2 years	Lithium may rarely cause hypercalcaemia and hypermagnesium
<b>Parathyroid Hormone (PTH)</b>			Measure only if serum calcium is elevated. PTH must be interpreted relative to serum calcium measurement on the same specimen
<b>Weight</b>	Baseline weight	Monthly, reduce frequency after 6–12 months if weight is stable	Encourage self-monitoring and weight control measures
<b>Pregnancy Test</b>	Baseline in women of childbearing age		
<b>ECG</b>	Baseline in patients with cardiac problems or aged over 45 years	12-monthly in patients with cardiac problems or aged over 45 years	Conduct more frequently if clinically indicated

\*The bpac creatine clearance calculator is based on the Cockcroft-Gault equation



## Drug interactions

Some drugs can raise serum concentrations of lithium and increase the risk of toxicity (Table 3). These include:

- Diuretics (mainly thiazides, but frusemide can also interact)
- NSAIDs, including over-the-counter preparations
- ACE inhibitors (e.g. cilazapril or quinapril) and ARBs (e.g. candesartan or losartan)

Generally, the interactions with NSAIDs, ACE inhibitors and ARBs are unpredictable and do not occur in all patients so concurrent use is not contraindicated. However, careful monitoring is required as cases of life threatening toxicity have been reported. Increases in lithium concentrations are delayed, taking several days to weeks to manifest, and monitoring should reflect this. Thiazides (e.g. bendrofluzide, hydrochlorothiazide) cause a more rapid (usually within three days) and predictable increase in lithium concentrations. Loop diuretics such as frusemide are much less likely to interact with lithium.

In addition to the above pharmacokinetic interactions, a number of drugs may enhance the adverse or toxic effects of lithium without a change in serum concentration. These include antidepressants, anticonvulsants, antipsychotics and calcium channel blockers. Concurrent use with SSRIs, tricyclic antidepressants and venlafaxine is usually uneventful and lithium is sometimes used to augment antidepressant effects. SSRIs and other drugs with serotonergic activity such as clomipramine, tramadol and venlafaxine have the potential to cause serotonin syndrome when combined with lithium, as lithium has some serotonergic activity. Patients should be monitored for signs of serotonin syndrome such as confusion, agitation, restlessness, sweating, nausea, diarrhoea, fever, hyperreflexia, tachycardia, myoclonus, lack of co-ordination, shivering and tremor and should be warned to report these immediately if they occur.

**Table 3 Drugs which may alter serum concentrations of lithium (Adapted from Stockley, 2006)**

	<b>Affect on serum lithium concentrations</b>	<b>Comments and management</b>
<b>NSAIDs and COXIBs</b>	Not always clinically significant. Usually occurs in the first week after addition of NSAID.	Risk increased in elderly, volume depletion, dehydration, changes in fluid/salt intake. Avoid concurrent use if possible. Check lithium concentrations weekly for first month and advise patient to report symptoms of lithium toxicity.
<b>Diuretics</b>	Thiazide and related diuretics (e.g. indapamide) can cause a rapid rise in serum lithium concentrations leading to toxicity. Not always clinically significant. Increased lithium concentrations usually occur within 7–10 days. Frusemide can also interact but this is less common.	Check lithium concentrations for at least two weeks after diuretic is started. Avoid in high risk patients such as the elderly and those susceptible to dehydration. Advise patient to report symptoms of lithium toxicity.
<b>ACE inhibitors and ARBs</b>	Not always clinically significant but two to four fold increases have been reported. Increase may be delayed by several weeks. One analysis found an increased relative risk of 7.6 for lithium toxicity requiring hospitalisation in elderly patients newly started on an ACE inhibitor.	Risk increased in elderly, volume depletion, heart failure, dehydration, changes in fluid/salt intake. Check lithium concentrations weekly for first 4–6 weeks and advise patient to report symptoms of lithium toxicity.
<b>Theophylline</b>	Serum lithium concentrations are reduced by 20 to 30% by the concurrent use of theophylline, which may cause patients to relapse. Caffeine may have a similar effect.	Serum lithium concentrations should be monitored if theophylline is stopped, started or if the dosage is altered. Also monitor if there is a significant change in caffeine intake.

## **Continuation and maintenance treatment**

There is debate in the literature about how long mood stabiliser treatment should be continued and various criteria have been proposed. Local consensus is to continue treatment for at least six months after a first manic episode. The criteria for long-term maintenance treatment varies but commonly includes at least two episodes of mania or depression.<sup>1</sup>

## **Discontinuing lithium treatment**

Discussion about discontinuing lithium treatment will usually be done in consultation with a specialist. Indications for discontinuing treatment include:

- Lack of response, given an adequate dose for an adequate time period.
- Renal failure or worsening renal insufficiency.
- Cardiac insufficiency.
- Ongoing poor compliance with medication (where interventions to improve compliance have been ineffective).
- Intolerable adverse effects to lithium.
- Remission of bipolar disorder for an adequate period of time in liaison with specialist (see below).

Early relapse of bipolar disorder (particularly mania) may occur after discontinuing lithium treatment. If it is withdrawn in under two weeks, the risk of relapse within the next three months is much higher than with slower withdrawal. Lithium should be reduced slowly over at least two weeks (ideally over four weeks) when being discontinued.

## **Cautions and contraindications to lithium treatment**

Lithium is contraindicated in patients with renal failure, cardiovascular insufficiency, Addison's disease and untreated hypothyroidism. For patients with less severe renal impairment, careful consideration of the risks and benefits of lithium treatment is required. Consultation with a renal physician may be of assistance.

It is strongly recommended that lithium therapy be carefully reviewed on an individual patient basis before a planned pregnancy. This will need to be done in liaison with a psychiatrist and/or maternal mental health services.

Care should be taken in patients who have vomiting or diarrhoea or if fluid or salt (sodium) intake is increased or decreased. This may include situations where patients have increased sweating such as during summer when exercise is increased, with infection or illness or if sudden dietary changes are made. Lithium serum levels may change significantly in these circumstances so more frequent monitoring may be required.

## Cases

### Case 1

MT, a 35 year old male with bipolar disorder has been stable on 800 mg daily of lithium carbonate and 10 mg daily of enalapril for six months with no apparent problems. His usual maintenance lithium concentration is 0.8 mmol/L. He presents to the surgery complaining of dizziness, ataxia and increased tremor. A lithium concentration of 1.6 mmol/L is reported and confirms drug toxicity. On questioning MT reveals that he has recently taken up strenuous exercise at the gym and has also been taking diclofenac, bought over-the-counter, for muscle aches.

Toxicity could have been precipitated by dehydration and excessive sweating as these can increase lithium concentrations. In addition the NSAID can also increase the concentration especially if MT is dehydrated. Enalapril can also interact but MT has been stable on this combination. The addition of the NSAID may have exacerbated the interaction.

The diclofenac was stopped and the lithium and enalapril withheld for 24 hours and re-checked. MT was advised to avoid dehydration while exercising and to take it a bit easier until his body adjusts. After 24 hours the lithium concentration was 0.9 mmol/L and re-stabilised on the same daily dose at 0.85 mmol/L. The enalapril was restarted when lithium concentrations stabilised and did not affect subsequent measurements.

### Case 2

AG, a 56 year old woman with recurrent major depression, responded well to the addition of 500 mg of lithium carbonate to her previous 125 mg of nortriptyline. During initial follow-up after this change there appeared to be no new side effects due to the lithium. Some three years later AG disclosed that she had ceased the lithium and found she was no longer having to rise four to five times during the night to pass urine, with resulting sleep disturbance.

Polyuria is generally a late side effect of treatment. Specific routine enquiry into such side effects is easily overlooked, but is important. Should continued treatment be indicated, consideration could be given to use of DDAVP nasal spray.

## References

1. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder. *Aust NZ J Psychiatry* 2004;38:280-305.
2. Australian and New Zealand clinical practice guidelines for the treatment of depression. *Aust NZ J Psychiatry* 2004;38:389-407.
3. Plenge P, et al. Lithium treatment: does the kidney prefer one daily dose or two? *Acta Psychiatr Scand* 1982;66:121-8.
4. Gitlin M. Lithium and the kidney: an updated review. *Drug Safety* 1999;20:231-243.
5. Henry C. Lithium side-effects and predictors of hypothyroidism in patients with bipolar disorder: sex differences. *J Psychiatry Neurosci* 2002;27:104-7.
6. Livingstone C, Rampes H. Lithium: a review of its metabolic adverse effects. *J Psychopharmacol* 2006;20:347-55.
7. Bendz H, Aurell M. Drug induced diabetes insipidus: incidence, prevention and management. *Drug Safety* 1999;21:449-456.
8. NHS. Guidelines for the management of patients on lithium. 2001.
9. Waitemata District Health Board. Lithium best practice guidelines. Medicines and Administration Manual. 2006.
10. Baxter K (Ed), *Stockley's Drug Interactions*. London: Pharmaceutical Press. Electronic version (2006).