

## Metabolic adverse effects of lithium

|                                       |   |
|---------------------------------------|---|
| <b>Thyroid disorders</b>              | <p>Hypothyroidism is common and is seen more frequently in women than men.<sup>5</sup></p> <p>Biochemical changes identical to those in primary hypothyroidism.</p> <p>Risk factors include elevated thyroid autoantibodies or TSH at baseline, family history, middle age, high lithium concentrations.</p> <p>Overt hypothyroidism is treated with thyroxine replacement. Management of subclinical hypothyroidism may be beneficial.</p> <p>Hyperthyroidism reported but relatively rare.</p>  |
| <b>Weight gain</b>                    | <p>Significant weight gain is common and may lead to reduced compliance.<sup>6</sup></p> <p>Reported risk factors include high baseline weight, young age, female gender and concurrent antidepressants.</p> <p>The mechanism may involve increased intake of high calorie drinks to relieve thirst.</p> <p>Weight gain or oedema should not be treated with diuretics.</p> <p>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>  |
| <b>Nephrogenic diabetes insipidus</b> | <p>Lithium is the most common drug cause, affecting 10% of patients treated for 15 years or more.<sup>7</sup></p> <p>Risk correlates with duration of lithium treatment.</p> <p>Presents as polydipsia and polyuria (24 hour urine volume &gt; 3 L).</p> <p>Dehydration, lithium intoxication and deteriorating renal function may occur and renal impairment may be permanent.</p> <p>Risk factors include long term treatment, concurrent use of long term NSAIDs, chronic physical illness and increasing age.</p> <p>Avoidance includes careful monitoring and awareness of risk factors. Management may include shared care with renal specialist and switch to alternative treatment.</p> |
| <b>Hyperparathyroidism</b>            | <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></p> <p>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.</p> <p>Corrected calcium levels above 2.75 mmol/L would usually warrant discussion with a renal physician.</p>  |

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

|  | Baseline  | Routine maintenance  | Comments  |
|--|---|--|---|
| <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.<br>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.<br>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

## Drugs which may alter serum concentrations of lithium (Adapted from Stockley, 2006)

|                                | Affect on serum lithium concentrations  | Comments and management  |
|--------------------------------|---|--|
| <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.  |

### 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.