

## Lithium Revisited – Frequently Asked Questions

Graylands Hospital Drug Bulletin 2004 Vol. 12 No. 4 December ISSN 1323-1251

- ★ Lithium has been utilised in the treatment of mania-related mental illnesses for over 50 years.
- ★ Although certain precautions, drug interactions or adverse effects may limit lithium's use in some patients, it is still widely used for the prophylaxis and treatment of mania and hypomania, recurrent depression and bipolar affective disorder.
- ★ This bulletin covers some of the pertinent points that are still applicable to lithium today and also some frequently asked questions with regard to lithium therapy.

### Does Alcohol interact with Lithium?

As noted in the Therapeutic Guidelines Psychotropic 2003, there is no specific interaction between lithium and alcohol<sup>1</sup>. A paper from 1985 found that consuming alcohol whilst taking lithium, may increase lithium levels, although only minimally<sup>2</sup>. The authors concluded that overall, alcohol appeared to have minimal effects on the pharmacokinetics of lithium<sup>2</sup>.

There is also some limited evidence to suggest that lithium carbonate combined with alcohol may make car driving more hazardous<sup>3</sup>. However, the evidence also suggests that lithium on its own, may increase the risk of a car crash, especially in elderly patients<sup>3,4</sup>. It would therefore be advisable for any patients taking lithium not to have any alcohol before driving a vehicle.

The central depressant effects of alcohol are enhanced when taken with sedative psychotropic medications such as benzodiazepines, antipsychotics and sedating antidepressants. Although this direct interaction does not occur with lithium and alcohol, a prescriber may not consider alcohol appropriate in a patient taking lithium for other reasons. These may include alcohol overuse leading to dehydration and

lithium toxicity or possible detrimental effects of alcohol on a patient's mental state.

### Can Lithium cause Cognitive Impairment?

The product information for lithium and Meyler's Side Effects of Drugs 14<sup>th</sup> Ed, both mention that mild cognitive impairment may occur with lithium use, but they do not give an incidence of this occurrence<sup>5,6</sup>.

Meyler's suggests it is difficult to determine whether these cognitive effects are due to the lithium, the disease process itself, or the effect of other medications that may be used, eg. benzodiazepines<sup>6</sup>.

Two reviews on the cognitive side effects of lithium found that, overall, lithium appeared to have a negative effect on the speed of information processing and that many patients complained of mental slowness, although there were inconsistent findings and limited adequate studies<sup>7,8</sup>.

One review concluded that based on a small number of well designed, controlled studies, that lithium had a negative effect on memory<sup>7</sup>. It postulated that inconsistent findings concerning memory effects were likely to be related to differences in methodology and research design<sup>7</sup>.

The other, more recent review, found a trend toward impaired verbal memory, though no impairment on tasks of visuo-spatial constructional ability or attention/ concentration was noted<sup>8</sup>.

### **Can Lithium Affect Renal Function?**

There has been some concerns that long-term treatment with lithium may cause nephrotoxicity.

The link between lithium and more serious renal adverse effects, such as changes to glomerular filtration rate or renal failure, has been disputed and remains controversial<sup>9,10</sup>.

It appears that in the majority of people, the long-term renal effects of lithium are benign<sup>11</sup>. There are however, reports of long-term lithium treatment leading to a reduction in glomerular filtration rate and renal insufficiency in a proportion of patients<sup>11,12,13</sup>. This risk may increase with the duration of lithium treatment<sup>12,14,15</sup>.

In spite of this, it is still unclear whether there is a definite link between lithium and progressive renal insufficiency<sup>6</sup>.

There is conflicting evidence on whether effects on the kidney may be lessened by single daily dosing of lithium. Some data suggests that once-daily lithium dosing may be less harmful to the kidney structure than when it is administered twice daily or more<sup>16</sup>. The authors of this study postulated that a number of kidney regenerative processes may only occur in periods of low lithium concentrations, which are less likely with twice daily lithium dosing<sup>16</sup>. More recent data however suggests that dosing strategy does not consistently affect renal function<sup>17</sup>.

### **Lithium and Diabetes Insipidus?**

Nephrogenic diabetes insipidus (NDI) is a condition where the kidneys do not respond to the action of antidiuretic hormone (ADH). Lithium affects renal concentrating ability which can lead to polyuria and more seriously NDI<sup>6</sup>.

Lithium-induced NDI is reversible in the short-term, but may be irreversible after long-term treatment (>15years)<sup>11,18</sup>. In some cases it is necessary to cease lithium, however some

patients can be managed by a reduction in lithium dose<sup>18</sup>.

Hypernatraemia, hypokalaemia and hypercalcaemia should be corrected if present and pharmacological treatment usually consists of a diuretic or non-steroidal anti-inflammatory drug (NSAID)<sup>18,19</sup>.

Amiloride (a potassium-sparing diuretic) and thiazide diuretics are utilised as they decrease extracellular fluid and promote proximal tubular resorption, which is not dependent on ADH<sup>18</sup>.

NSAIDs, in particular indomethacin, are thought to help by promoting water resorption and/or decreasing the glomerular filtration rate (resulting in less urine flowing into the distal tubule and less loss of free water)<sup>18</sup>.

Care should be taken if using an NSAID and/or a diuretic as both can decrease lithium clearance, thereby increasing the risk of lithium toxicity.

### **Can Lithium cause Cardiac Adverse Effects?**

Lithium-induced cardiovascular effects can occur in 20-30% of patients, but they are usually benign<sup>20,21</sup>. Changes in the electrocardiogram (ECG), decreases in heart rate, congestive myopathy, and rarely arrhythmias and sinus node dysfunction have been reported<sup>20,21</sup>.

A baseline ECG is recommended for all patients commencing on lithium and the product information lists significant cardiac disease as a contraindication for lithium use.

### **What Factors Affect Lithium Levels?**

As lithium has a narrow therapeutic index, regular monitoring of serum level concentrations are important. Lithium levels are usually maintained between 0.5-1.2mmol/L for acute mania and between 0.4-1.0mmol/L for prophylaxis<sup>22</sup>.

The recommended therapeutic lithium concentration in the literature are based on trough concentrations, assuming a patient is taking lithium twice daily (12-hourly) and is at steady state, i.e. has been taking lithium at a constant dosage for at least 5 half-lives. (The half-life of lithium varies, but it should have reached steady state by 5-7 days).

Trough levels should be taken 12 hours after the last dose, just prior to the next dose being given, preferably at the same time of day each time.

Patients who are taking lithium as a once daily night-time dose, will have 10-25% higher 12-hour serum concentrations than those seen with twice-daily dosing<sup>1</sup>. Therefore correspondingly higher 12-hour serum concentrations should be aimed for in these patients<sup>1</sup>.

There is no any clear comparative data between immediate and sustained release lithium to determine whether the different preparations available in Australia may alter the lithium level.

Renal impairment reduces the clearance of lithium, thus increasing lithium levels. Dehydration, and any illness that may cause dehydration, will lead to sodium depletion and therefore increase lithium levels. Similarly, if a patient is on a low-sodium or sodium-free diet, their lithium levels will be increased. Conversely, if a patient's sodium intake increases, their lithium levels will decrease.

Pregnant patients have increased lithium clearance, therefore lithium levels will be decreased. Immediately after delivery, lithium clearance drops, causing lithium levels to rise.

Drug interactions are important factors in altering lithium levels. There are many medications that interact with lithium, however the most commonly prescribed would include NSAIDs, diuretics and ACE inhibitors, which can all increase lithium levels.

There is also a published case report where serum lithium levels were altered due to significant inaccuracies in a laboratory's equipment<sup>23</sup>.

### **Lithium Levels in the Brain?**

The brain:serum ratio is usually considered to be fairly constant at 1:1, but it can vary widely. One study found that brain:serum ratios ranged from 0.51-1.23, with a mean of 0.8<sup>24</sup>. There have been reports however of brain:serum ratios of as varied as 100:1<sup>21</sup>.

It has been suggested that treatment response is more closely related to the lithium concentration in the brain, than to serum concentration<sup>25</sup>. This

reason, along with variability in brain:serum ratios, may explain why some patients show differing responses at therapeutic serum levels and why some may experience adverse effects at low doses.

A small study found that brain:serum concentrations ratios were lower in children and adolescents, than in adults<sup>26</sup>. The authors suggest that children and adolescents may need higher maintenance serum lithium concentrations, to ensure that brain lithium concentrations reach therapeutic levels<sup>26</sup>.

### **Can Lithium SR be Cut in Half?**

Sustained release lithium is available in Australia as the preparation Quilonum SR® (450mg tablets). Quilonum SR® has an indication for twice daily dosing, every 12 hours. The tablets are not enteric-coated or "controlled-release". The tablets have a slowed dissolution rate due to the physicochemical properties of the carbonate salt and the relative presence of inactive ingredients in the tablet.

The Therapeutic Goods Administration (TGA), does not have bioavailability data for half a Quilonum SR® tablet, therefore the drug company that supplies Quilonum SR® cannot promote the breaking of tablets.

As the tablets are not enteric coated nor controlled release, they can theoretically be broken in half, however they should not be crushed or chewed, as this would reduce the delayed disintegration properties of the tablet.

### **Lithium and Thyroid Function?**

It is well known that lithium increases the incidence of thyroid dysfunction. Hypofunction is the most common abnormality and can present as an abnormal test result, goitre without hypothyroidism or symptomatic hypothyroidism<sup>27</sup>.

Serum levels of lithium are not thought to correlate with incidence and severity of hypothyroidism. In rare cases, lithium has been associated with *hyper*thyroidism. A recent Graylands Hospital Drug Bulletin (Vol 11, No3, June 2003) outlines when treatment is required for lithium-induced hypothyroidism<sup>27</sup>.

## What is Lithium Orotate?

Lithium orotate is a lithium salt that is available without a prescription, on its own or in combination products. It is generally sold from healthfood-type stores and is readily available over the internet.

Its claims include having greater bioavailability than other lithium salts, giving relief from symptoms of certain mental illnesses without the risk of side-effects and no need for lithium levels to be conducted.

There is virtually no published human research on the use of lithium orotate, so no evidence-based recommendations can be made about its use. It appears that the vastly varied claims made of its benefits are based on a single study from 1971 that involved testing in a rat's brain.

There is no evidence to suggest that lithium orotate is effective in the treatment of mania-related mental illnesses, or that it is completely free of adverse effects. It can also be considerably more expensive for the patient than lithium carbonate.

## Graylands Lithium Monitoring Guidelines

- Patients commencing lithium: U+E, TFT, ECG, and pregnancy test
- Commence lithium at 250 to 1000mg orally, daily, initially in two or three divided doses and titrate to therapeutic range according to levels (after 5 to 7 days of steady dosing)
- Monitor serum lithium levels 5 to 7 days after starting or changing a dose
- Maintain serum lithium level between 0.5 to 1.0mmol/L (sample should be taken 12 hours post dose, withhold on morning of blood test)
- All patients commenced on lithium should be provided with full information on lithium treatment and this education recorded in the patient's notes.
- Patients admitted on lithium, check: serum lithium level, U+E, TFT
- Monitor serum lithium levels, and U+E every 3 to 6 months during maintenance therapy and when clinically indicated
- Monitor TFT every 6 to 12 months and when clinically indicated

## References:

1. Psychotropic Writing Group. Therapeutic Guidelines: Psychotropic. North Melbourne: Therapeutic Guidelines Ltd; 2003.

2. Anton RF, Paladino JA, Morton A, Thomas RW. Effect of acute alcohol consumption on lithium kinetics. *Clin Pharmacol Ther* 1985; 38:52-55.
3. Linnoila M, Saario I, Maki M. Effect of treatment with diazepam or lithium and alcohol on psychomotor skills related to driving. *Eur J Clin Pharmacol* 1974;7: 337-342.
4. Etmiman M, Hemmelgarn B, Delanet JAC, Suissa S. Use of lithium and the risk of injurious motor vehicle crash in elderly adults: case-control study nested within a cohort. *BMJ* 2004; 328:558-559.
5. Lithicarb® Product Information. St Leonards: Aspen Pharmacare Australia Pty Ltd, February 23, 2004
6. Jefferson JW. Lithium. In: Dukes MNG, Aronson JK, editors. *Meyler's Side Effects of Drugs*. 14<sup>th</sup> ed. Amsterdam: Elsevier Science BV; 2000. p. 86-94.
7. Honig A, Arts BMG, Ponds RWHM, Riedel WJ. Lithium induced cognitive side-effects in bipolar disorder: a qualitative analysis and implications for daily practice. *Int Clin Psychopharmacol* 1999; 14:167-171.
8. Pachet AK, Wisniewski AM. The effects of lithium on cognition: an updated review. *Psychopharmacology* 2003; 170: 225-234.
9. Schou M. Forty years of lithium treatment. *Arch Gen Psychiatry* 1997; 54(1): 9-15.
10. Povlsen UJ, Hetmar O, Ladefoged J, Bolwig TG. Kidney functioning during lithium treatment: a prospective study of patients treated with lithium for up to ten years. *Acta Psychiatr Scand* 1992; 85:56-60.
11. Gitlin M. Lithium and the kidney: an updated review. *Drug Safety* 1999;20(3): 231-243.
12. Lepkifker E, Sverdluk A, Iancu I, Ziv R, Segev S, Kotler M. Renal insufficiency in long-term lithium treatment. *J Clin Psych* 2004; 65(6): 850-856.
13. Turan T, Esel E, Tokgoz B, Aslan S, Sofuoglu S, Utas C et al. Effects of short- and long-term lithium treatment on kidney functioning in patients with bipolar mood disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26(3): 561-565.
14. Presne C, Fakhour F, Noel LH, Stengel B, Even C, Kreis H et al. Lithium-induced nephropathy: rate of progression and prognostic factors. *Kidney Int* 2003; 64(2): 585-592.
15. Bendz H, Aurell M, Lanke J. A historical cohort study of kidney damage in long-term lithium patients: continued surveillance needed. *Eur Psychiatry* 2001; 16(4): 199-206.
16. Plenge P, Mellerup ET, Bolwig TG, Brun C, Hetmar O, Ladefoged J et al. Lithium treatment: does the kidney prefer one daily dose instead of two? *Acta Psychiatr Scand* 1982; 66:121-128.
17. Abraham G, Waldron JJ, Lawson JS. Are the renal effects of lithium modified by frequency of administration? *Acta Psychiatr Scand* 1995; 92:115-118.
18. Stone K. Lithium-induced nephrogenic diabetes insipidus. *J Am Board Fam Pract* 1999; 12(1):43-47.
19. Beers MH, Berkow R, editors. *The Merck Manual of Diagnosis and Therapy*. New Jersey; Merck Research Laboratories; 1999.
20. Dunner D. Optimizing lithium treatment. *J Clin Psychiatry* 2000; 61 [suppl 9]: 76-81.
21. Bazire S. *Psychotropic Drug Directory*. United Kingdom: Fivepin Publishing Ltd; 2003
22. Editorial Advisory Board. *Australian Medicines Handbook*. Adelaide: Australian Medicines Handbook Pty Ltd; 2004.
23. Lovell RW, Bunker WW. Lithium assay errors. *Am J Psychiatry* 1997; 154(10): 1477.
24. Sachs GS, Renshaw PF, Lafer B, Stoll AL, Guimaraes AR, Rosenbaum JF et al. Variability of brain lithium levels during maintenance treatment: a magnetic resonance spectroscopy study. *Biol Psychiatry* 1995; 38:422-428.
23. Bazire S. *Psychotropic Drug Directory*. United Kingdom: Fivepin Publishing Ltd; 2003.
25. Kato T, Inubushi T, Takahashi S. Relationship of lithium concentrations in the brain measured by lithium-7 magnetic resonance spectroscopy to treatment response in mania. *J Clin Psychopharmacology* 1994; 14(5):330-335.
26. Moore MC, Demopoulos CM, Henry ME, Steingard RJ, Zamvil L, Katic A et al. Brain-to-serum lithium ratio and age: an in vivo magnetic resonance spectroscopy study. *Am J Psychiatry* 2002; 159:1240-1242.
27. Lithium-induced hypothyroidism, when to treat? *Graylands Hospital Drug Bulletin* 2003; 11(3).

## Acknowledgment

This article was prepared by Anouska Feszczur and reviewed by the Pharmacy Department.

Comments are welcome at the e-mail address:  
[DrugInformation.Graylands@health.wa.gov.au](mailto:DrugInformation.Graylands@health.wa.gov.au)