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Lithium therapy

I. N. Ferrier, S. P. Tyrer & A. J. Bell

Since the introduction of lithium therapy 30 years ago it has become a major weapon in psychiatrists' armamentarium. It is the drug of first choice for the prevention of recurrent mood disorders, and it is estimated that about one person in every thousand people in Britain receives lithium at any one time. It therefore behoves doctors to be familiar with its use. This article is not a comprehensive account of the pharmacology of lithium (for this the reader is referred to Johnson (1987) and Peet & Pratt (1993)) but concentrates on its clinical use in practice and some less well known, but important, phenomena.

Indications for use

Prevention of recurrent affective disorder

Lithium is the primary agent in the prophylaxis of bipolar affective disorder. Comparative trials have been carried out with other agents, most frequently with carbamazepine and sodium valproate, but no definite advantage has been shown with the alternative drugs except in complicated disorders (such as rapid cycling affective disorder), and lithium remains the first choice for initial treatment (Hopkins & Gelenberg, 1994). There is increasing evidence for the usefulness of anti-convulsants alone or in combination with lithium in poor outcome patients, but the details are outside the scope of this article.

There are few absolute contraindications to giving lithium, as dosage adjustment and careful monitoring normally allow patients who have compromised medical health to receive lithium. Relative contraindications include administration during pregnancy, in particular the first trimester; variable renal function; second or third degree heart block; and conditions that cause electrolyte imbalance, in particular hyponatraemia.

The decision about when to institute lithium treatment in a patient with mood disorder depends upon the severity and frequency of previous episodes of illness, the effect future episodes are likely to have on the patient's functioning, and family history of affective illness. As the onset of mania can be devastating to domestic and occupational life, the indications for treatment by lithium in bipolar disorder are stronger than in unipolar illness. If two discrete episodes of mania or depression occur within a three year period, lithium should normally be given unless there are contraindications (Grof *et al*, 1978). In patients with recurrent depression it is usual to consider lithium after three episodes of illness. However, the decision on when to start lithium depends above all on discussion with the patient of the risks involved of recurrence of illness and the impositions of lithium treatment. It may be advisable to give prophylactic lithium after only one manic episode when a further manic attack could have profound social and/or financial consequences.

Use in other conditions

Lithium is effective in acute mania (but there is a lag period of 5–7 days before major effects are shown); in the augmentation of antidepressants; in the treatment of resistant depression; and in cluster headache. It inhibits DNA viruses. Lithium reduces impulsive aggression in patients with organic brain damage (Tyrer, 1994) and has a licensed indication for aggression in those with learning disability. It has been used in the treatment of schizophrenia, particularly when affective symptoms are prominent, and may improve the response of schizophrenic patients to neuroleptic drugs (Jefferson, 1990).

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Augmentation in depression

In patients who have been treated with adequate doses of antidepressants for at least a four-week period, in whom compliance is assured and in whom no or inadequate response has been obtained, addition of lithium has been shown to improve depression (de Montigny *et al*, 1983). Although initial studies suggested that the addition of lithium improved depression considerably within one week, later studies suggest that it may be necessary to give lithium for at least four weeks before assuming lack of response (Price *et al*, 1986).

In a patient with a normal serum creatinine it is usual to add 400 mg of lithium at night to the existing antidepressant dose regime and measure serum lithium levels after one week. If this level is below 0.4 mmol/l, the dosage of lithium can be increased to 600 mg or 800 mg nocte and the patient maintained on this dose. Lithium levels should be maintained within the therapeutic range of 0.4–0.8 mmol/l for at least four weeks before deciding on alternative treatments.

Lithium can be added to selective serotonin reuptake inhibitors (SSRIs) and MAOIs with improvement in depression. Isolated reports of the serotonergic syndrome (agitation, hyperpyrexia and myoclonus) have been documented. It is wise to keep the doses of SSRIs and lithium at the lower end of the recommended range.

On the basis of case reports and two retrospective studies (Small & Millstein, 1990) it has been suggested that lithium should be withdrawn before starting ECT in order to avoid neurotoxicity, and it should not be re-instated for several days following the last convulsive treatment.

Initiation of treatment

Before starting treatment a full medical history should be taken and appropriate investigations carried out. Examination should include measurement of body weight, blood pressure and, if there is any suggestion of cardiac symptoms or abnormality, an electrocardiogram should be performed. Serum thyroxine and TSH level, serum creatinine and electrolyte analysis should be carried out in every case. It is not normally necessary to carry out creatinine clearance estimations unless there is evidence from the history or examination of impaired renal function.

Box 1. Tests before starting lithium treatment
1. Measure blood pressure.
2. ECG if any cardiac symptoms, particularly if patient is over 50 years.
3. Measure weight and serum thyroxine, TSH, creatinine and electrolytes.
4. Give information leaflet regarding lithium to patient.

Before starting treatment each patient should be given an information pamphlet about the use of lithium treatment and the reasons for monitoring its prescription. It is important to record administration of these instructions in the case notes and it may be advisable for the patient to endorse having received this information and discussion about the use of lithium (Birch *et al*, 1993).

Lithium preparations and treatment regime

Lithium is normally administered in tablet or capsule form but a syrup is available. The preparations most frequently used in the UK are Priadel and Camcolit. These preparations are available in 200 mg and 400 mg strengths and have comparable bioavailability. A slower-release preparation, Litarex, containing lithium citrate, is available and is preferred if nausea and early gastro-intestinal symptoms are a problem.

It is usual to start lithium by giving a dosage of 0.15–0.20 mmol/kg/day (i.e. about 400–600 mg/day of lithium carbonate or 1000–1500 mg/day of lithium citrate in a person weighing 70 kg), and measuring serum lithium concentration one week later, when steady-state conditions have normally been reached. The dosage can then be adjusted to the desired steady-state concentration as there is a direct relationship between dose and serum lithium level. Thus, if a daily maintenance dose of 1200 mg of lithium per day produces a steady state concentration of 0.9 mmol/l, a dosage of 800 mg will result in a concentration of 0.6 mmol/l.

Patients with acute mania require greater doses of lithium to maintain therapeutic serum lithium levels and a corresponding starting dose in a 70 kg patient with mania would be about 1000 mg of lithium carbonate. This dose should be given in divided doses in mania, although in prophylaxis a single night-time dose is preferred to increase compliance.

It is possible, but not usually necessary, to

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determine the dosage regime in an individual patient by using the serum lithium concentration measured after a single loading dose of lithium carbonate combined with prediction tables (Perry *et al*, 1986; Aronson & Reynolds, 1992).

The normal maintenance serum lithium range is between 0.5 and 0.8 mmol/l. Serum lithium concentrations lower than 0.4 mmol/l are not effective in the majority of patients; serum concentrations over 1.0 mmol/l are more likely to be accompanied by side-effects and render the patient liable to neurotoxicity.

In order to achieve standardisation of serum lithium levels, blood for serum lithium should be taken 12 hours after the last dose of the drug. In practice, intervals of between 11 and 14 hours between the dosage and venepuncture are acceptable, although if blood is taken more than an hour outside the 12-hour period the timing of the blood sample should be recorded.

Monitoring of treatment

As the therapeutic ratio (serum level achieving therapeutic benefit: toxic serum lithium level) is low, it is essential to monitor serum lithium levels closely. The recommended range of serum lithium levels to achieve therapeutic efficacy varies according to the condition for which lithium is being given. For the prophylactic treatment of recurrent depression the dose of lithium should be adjusted to maintain a 12-hour serum lithium level of between 0.5–0.8 mmol/l. It has been shown in bipolar patients that the risk of relapse is reduced 2.6 times if lithium levels are maintained between 0.7–0.9 mmol/l, but compliance is poorer with this regime (Gelenberg *et al*, 1989).

For the acute treatment of mania retrospective evidence suggests that a serum lithium level of between 0.9–1.4 mmol/l is necessary (Prien *et al*, 1972), and once there is normalisation of mood the dosage of lithium can be reduced. Serum lithium monitoring should be carried out frequently over this period.

Once a patient is maintained on lithium, serum lithium levels should be determined immediately if there is a suggestion of lithium toxicity or affective relapse. If the patient's condition remains stable, lithium levels should normally be checked at one or two-monthly intervals within the first six months of starting the drug, but if lithium levels are stable and the patient's insight is good the monitoring interval can be extended to six months (three months in elderly patients).

There is little consensus on these figures and little evidence that checking lithium levels more frequently is helpful in the long run – some argue that monitoring of the side-effects and regular checks of renal function are all that is required. However, compliance may be enhanced by informing the patient that lithium itself is to be measured and the intervals stated seem prudent from the medico-legal standpoint.

Serum creatinine and thyroid function tests should be carried out at least once a year in patients receiving lithium treatment.

Measurement of lithium

Most laboratories carry out lithium analysis by flame spectrophotometry. It is usual to carry out lithium analysis on serum, so clotted blood should be used. A lithium ion-selective analyser is now available which allows determination of lithium in whole blood within a minute (Birch *et al*, 1993). If this apparatus is available the patient and doctor can discuss the results of the blood tests and compliance can be enhanced.

Reasons for possible lithium inefficacy

Unsatisfactory response to lithium treatment may have causes other than ineffective serum lithium concentration. The diagnosis of affective illness may not be correct; the drug may not have been given for a sufficient length of time (it may be necessary to continue treatment for three months before any therapeutic effect is obtained); and there may be irregular tablet intake. The most common reason for failure of lithium treatment is noncompliance, and it should be emphasised to patients starting lithium that drug therapy is a long-term commitment. It is wise to involve the patient's partner in discussions about lithium treatment and if there is concern about the patient's mental state or compliance with the drug regime, the partner should be given every encouragement to contact the clinician. It may be helpful to initiate a treatment plan where the patient agrees to comply with medication and monitoring for a set time (perhaps 3 years) with a full review being arranged at that time.

There is evidence that, in some patients, lithium becomes less effective over time (Post, 1993). Work from the same group suggests that there is reduced responsiveness to lithium when the drug is re-administered after a discontinuation-induced relapse. It is worth emphasising this latter point to a patient considering stopping the drug who believes that restarting the drug after any relapse will result in identical prophylactic efficacy.

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Early side-effects

Side-effects within the first five days of starting lithium treatment include thirst, abdominal discomfort, nausea, diarrhoea, a metallic taste, muscle weakness and fatigue. The frequency of these symptoms is related to serum lithium level, and ranges from 60% for thirst to 6% for diarrhoea at a mean serum lithium level of 0.7 mmol/l (Vestergaard *et al*, 1988). It is worthwhile warning the patient of these possibilities and stressing their transitory nature, so as to maximise compliance at a stage before any clinical benefit is seen.

Long-term side-effects

Lithium toxicity and neurotoxicity

The toxic effects of lithium salts on the central nervous system have been described for nearly a century. Toxic symptoms become increasingly common above serum levels of 1.2 mmol/l and occur in three main organ areas: cerebral, gastro-intestinal and cerebellar. Early signs are of mental lassitude or malaise occurring with or without agitation. This can progress to a confused state with vomiting and/or diarrhoea, coarse tremor, Parkinsonism and cerebellar signs (ataxia and dysarthria). The final stages are characterised by general disturbances of consciousness and neuromuscular function, seizures, coma and death. Long-term neurological defects (usually cerebellar) can result from acute lithium toxicity in about 10% of cases (Schou, 1984).

However, of concern to the clinician are the reports of clinically unpredictable cases of neurotoxicity occurring at therapeutic levels of lithium. The symptoms of lithium neurotoxicity at therapeutic levels are mostly neurological, and differ only in degree from those described in cases of toxicity with high levels. They can occur in both acute and chronic therapy; the most common presentation is one of an encephalopathy. Rarely, focal neurological disturbances (sensory and motor nerve palsies), motor disturbances, psychotic episodes (paranoia and visual/auditory hallucinosis), and specific cognitive deficits can occur (Verdoux & Bourgeois, 1990; Sheean, 1993; Bell & Ferrier, 1994).

Factors leading to toxicity and neurotoxicity

There are general factors, affecting all patients, which will produce a rise in serum lithium level with consequent toxic symptoms. These are relatively predictable and can be guarded against by careful monitoring and patient information. They arise from:

(a) Increased intake of lithium – prescription or patient error.
(b) Increased retention of lithium
  (i) Sodium depletion e.g. salt-free diets, vomiting and diarrhoeal illnesses, excessive sweating and dehydration
  (ii) Drug interactions e.g. thiazide diuretics, most nonsteroidal anti-inflammatory drugs (particularly indomethacin, ibuprofen, piroxicam, naproxen and phenylbutazone), and some antibiotics excreted by the kidney (erythromycin, metronidazole and tetracycline)
  (iii) Systemic illness – particularly cardiac failure, renal disease and any pyrexial or gastro-intestinal disturbance.

There are also individual specific factors which reduce lithium tolerance and are associated with neurotoxicity at much lower serum levels.

Some individuals seem to have a cerebral vulnerability and/or sensitivity to lithium. There have been reports of neurotoxic symptoms at therapeutic lithium levels in patients with pre-treatment EEG abnormalities (particularly temporal lobe epilepsy), schizophrenia or schizo-affective illnesses. Reversible neurotoxic reactions have also occurred in cases of previously unsuspected intracerebral pathology and in association with Parkinsonism and mild cognitive impairment in the elderly.

A separate category of subjects absorb more lithium intracellularly, probably as a result of inherited sodium pump deficiencies, and manifest by increased red blood cell (RBC) (and by implication intracerebral) lithium concentrations. Factors affecting this process are co-prescription of phenothiazines (particularly thioridazine), weight fluctuation and changes in the clinical state.

More potent neuroleptics, e.g. butyrophenones, have been associated with a neuroleptic malignant syndrome (NMS) picture. Particularly ominous is the co-existence of NMS with lithium neurotoxicity which has been associated with permanent cerebellar damage at levels of 0.9 mmol/l (Verdoux & Bourgeois, 1990).

Recently there have been a number of reports of severe neurotoxicity, when calcium channel blockers have been added to lithium. The unpredictability of this interaction suggests that close monitoring of clinical state and levels is required,

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and particular caution is advised in the elderly. This interaction is less likely if lithium levels are maintained at or around 0.5 mmol/l (Wright & Jarrett, 1991).

Management

Lithium therapy should be discontinued immediately in any patient with neurological signs (central or peripheral) or serious gastrointestinal disturbance. Patients should be told that if they feel unwell they can stop the drug for 24–48 hours without hazard. A serum level in the toxic range needs to be treated accordingly, but a therapeutic level does not exclude neurotoxicity. Confirmatory investigations include the EEG which shows increased theta and delta activity with diffuse slowing and background disorganisation; the RBC lithium level which normally should be less than 0.6 mmol/l; and the RBC/serum lithium ratio (normal range 0.3–0.5). Clinical improvement can take up to three weeks and is paralleled by improvement in the EEG.

The diagnosis of lithium toxicity has to be on clinical grounds rather than on the basis of blood results.

Tremor

Tremor is common in patients taking lithium and it is important for physicians to be able to recognise the different forms and react accordingly. It is noteworthy that tremor is one of the commoner reasons given by patients for discontinuing lithium.

Fine tremor. This occurs in about 15% of lithium-treated patients (Vestergaard *et al*, 1988). In most patients it is either transitory or sporadic (sometimes associated with anxiety) and balanced reassurance is helpful to the patient. It is usually seen in the outstretched hands and is rare elsewhere. In most cases the tremor does not interfere with function, but if it does then reduction of the dose to achieve a level of 0.5 mmol/l is helpful in the majority of cases. If the problem is persistent then β-adrenergic blockade (with the usual care) is helpful to some, but not all.

Flapping or coarse tremor. This tremor is associated with impending or established toxicity. Muscle fasciculation, myoclonus, cerebellar signs or athetoid movements are also ominous. These tremors are widespread and are usually, but not always, accompanied by other symptoms of toxicity. The presence of dysarthia with coarse tremor should set alarm bells ringing.

Pill-rolling tremor. A significant percentage of older patients on lithium, usually those with long exposure, complicated histories and poor outcome, develop either a Parkinsonian-like picture with tremor as a predominant feature, or a tardive dyskinesia type syndrome. Subclinical movement disorder may also be revealed by specific testing in these and less disabled patients. These clinical states may be associated with cognitive decline. The role of present or past neuroleptic medication is controversial but likely to be important. Anticholinergic drugs are ineffective. Reduction of the dose of any concomitant neuroleptic *and* of the lithium is recommended, and should precede any attempt to use dopaminergic agonists.

Box 2. Side-effects and toxicity - key learning points

1. The diagnosis of lithium toxicity should be made on clinical grounds rather than on the basis of blood results.
2. Hypothyroidism on lithium is common in women and requires active intervention. TSH is the most useful marker.
3. Renal function is unimpaired in the absence of episodes of toxicity but requires frequent monitoring.
4. Careful sympathetic assessment of side-effects increases compliance.

Thyroid disorders

It is well established that lithium therapy is linked to hypothyroidism and goitre in some patients. There are reports of hyperthyroidism occurring in lithium-treated patients but the number of cases is so few that it is likely the association is one of coincidence.

The frequency of lithium-induced hypothyroidism is unknown but current estimates put this risk at between 2 and 3%. As with non-lithium-induced hypothyroidism, this complication is found principally in middle-aged women – the female to male ratio of published reports is 9:1. The average duration of lithium therapy before the diagnosis of hypothyroidism is 18 months – there are however case reports of this occurring dramatically within a month of therapy.

Subtle changes in thyroid function occur frequently in patients who do not develop frank hypothyroidism. Serum thyroxine falls (although within the euthyroid range) and a slight rise in TSH is seen. However, these changes are transitory and values should return to normal after one year.

The presence of thyroid auto-antibodies is a strong indicator of the likelihood of developing frank hypothyroidism in patients on lithium (Bocchetta *et al*, 1992). These antibodies are found

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in about 10% of the normal population but the frequency of them rises steeply in women after the age of 45. Patients with auto-antibodies and/or raised TSH are at high risk of developing hypothyroidism. Measuring these before lithium is started is recommended and such patients need even closer monitoring (Myers *et al*, 1985). There is growing evidence that lithium may induce thyroid-antibody formation (Wilson *et al*, 1991), most probably in those already predisposed (Lee *et al*, 1992).

Regular monitoring of thyroid function in lithium-treated patients is recommended. Current suggestions are that this should be done yearly in men and six-monthly in women. The possibility of clinical hypothyroidism should be borne in mind particularly when reviewing a patient who has had a depressive relapse despite adequate lithium levels.

Once hypothyroidism has been diagnosed (even on biochemical grounds) treatment of the condition should be instigated rapidly. Most authors would agree that low/borderline T_4 should lead to thyroxine therapy, and some would argue that patients with normal T_4 but significantly raised TSH (e.g. over 10 mU/l) should be treated, especially if auto-antibodies are present. Referral to a physician is not usually necessary but is recommended in complicated cases, for example some elderly patients and those with cardiovascular disease. Discontinuation of lithium therapy is an option but in most cases the psychiatric indication for continuing it is strong. Even if lithium is stopped it is usually wise (unless the TSH rise is small) to treat the hypothyroidism and seek specialist advice. Treatment is normally with thyroxine with regular monitoring of TSH.

Goitre occurs in approximately 5% of lithium-treated patients – the frequency rises with length of treatment. It is not usually associated with hypothyroidism – a view supported by the slight male preponderance of cases. It is not usually of clinical concern and no case of lithium-associated thyroid malignancy has been reported. If the goitre enlarges then either lithium should be stopped or a small dose of thyroxine given.

Metabolic and other disturbances

A significant percentage of patients on lithium develop polyuria and polydipsia; this is a nephrogenic *diabetes insipidus*-like syndrome mediated by lithium's effect on cyclic AMP and the action of vasopressin. These effects are reversible and complications avoided by maintaining an adequate fluid and salt intake. If polyuria is troublesome a reduction in lithium level to 0.5 – 0.7 mmol/l and/or a change to a single daily dose may be helpful (although this is a matter of dispute). Long-term impairment of renal concentrating ability and/or pathological change in the kidney is seen only in patients who have episodes of lithium toxicity (Schou, 1988).

Long-term lithium therapy may be associated with a slight rise in serum calcium (about 2% after adjustment for protein) and a slight increase in parathyroid hormone secretion. Ionised calcium remains unchanged. Such a development is usually of no consequence but very rarely lithium therapy is associated with clinically significant hyperparathyroidism and so calcium should be monitored in patients with physical complaints.

Weight gain is seen in about a third of patients on lithium, is more common in women, and is an important cause of noncompliance. The mechanism remains unclear (no effect of dose reduction has been noted). No clinically relevant changes in liver or endocrine function are reported with lithium but there are a few case reports of sexual dysfunction in men (Johnson, 1987).

A rise in the while cell count (predominantly neutrophils) and, to a lesser extent, platelet count is seen in patients on lithium. The rise in WBC can be 30 – 45%, but rises of such magnitude are usually transitory; a 10% increase in counts is more usual in long-term therapy.

Discontinuation of lithium

Discontinuation of lithium is associated with an increased likelihood of relapse of affective illness. Mania is more likely to occur than depression in bipolar patients but depression is the rule in unipolar illness. The risk of relapse is increased if the patient has been taking lithium for a short time; it has been shown that unless lithium is given for at least two years at a dosage to maintain a therapeutic serum lithium level, the risk of an affective relapse is greater than if no treatment was given for the condition (Goodwin, 1994).

If a decision is made to discontinue lithium the risks of this procedure should be discussed in detail with the patient beforehand. It is important to discuss the signs and symptoms of relapse with the patient and their carers, and to encourage them to seek help early if necessary. It is advisable to reduce the dose of lithium slowly over a period of two to three months rather than stopping the drug suddenly, although even under these conditions there is an increased risk of manic relapse in bipolar patients (Tyrer *et al*, 1983).

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Multiple choice questions

1 In patients maintained on lithium the following tests should be carried out at least once a year:
- a serum sodium
- b ECG
- c serum thyroxine
- d serum creatinine
- e serum creatine kinase

2 Lithium withdrawal may result in:
- a increased risk of mania in bipolar patients
- b increased risk of relapse within two years of starting lithium
- c increased risk of renal complications
- d hypercalcaemia
- e neuroleptic malignant syndrome

3 The following have been associated with lithium neurotoxicity at normal serum levels.
- a constructional dyspraxia
- b cerebellar ataxia
- c facial nerve palsy
- d confusional state
- e complex partial seizures

4 In patients on lithium, hypothyroidism:
- a should be suspected if depression occurs in the presence of adequate levels
- b is more common in men
- c is likely if goitre is present
- d improves if serum levels are reduced to 0.5 mmol/l
- e is more likely if thyroid auto-antibodies are present

MCQ answers

1	2	3	4
a T	a T	a T	a T
b F	b T	b T	b F
c T	c F	c T	c F
d T	d F	d T	d F

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