

LITHIUM

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Lithium is used in the treatment of acute mania and in the prophylaxis of bipolar and unipolar affected disorders

Serum (prepared from clotted blood) and plasma (prepared from anticoagulated blood) can be used interchangeably for other drug measurements. However, serum is usually used for measurement of lithium to avoid potential interference from lithium heparin, which is used as an anticoagulant

Monitoring serum lithium concentrations is an important part of treatment in patients with acute mania as the drug's toxic:therapeutic ratio is very low and its pharmacokinetics vary from person to person, making accurate prediction of dosage difficult. The variation is due to differences in absorption, distribution, and elimination.

Absorption of lithium is highly variable, depending on the formulation used. The rate and extent of absorption varies between modified release and conventional formulations, but there is also variability from one modified release formulation to another.

The variations in the clearance and apparent volume of distribution of lithium result in variation in its half life from 7 hours to 41 hours.

In this article we apply to lithium the criteria which must be fulfilled in part or in full before measurement of its plasma concentration can be considered worth while.

Criteria for measurement

Is there difficulty in interpreting clinical evidence of the therapeutic or toxic effects?

Although it may be possible to achieve a steady state serum lithium concentration within the therapeutic range relatively rapidly (for example, by giving a loading dose), the onset of a detectable therapeutic action in patients with acute mania may be delayed for up to two weeks.

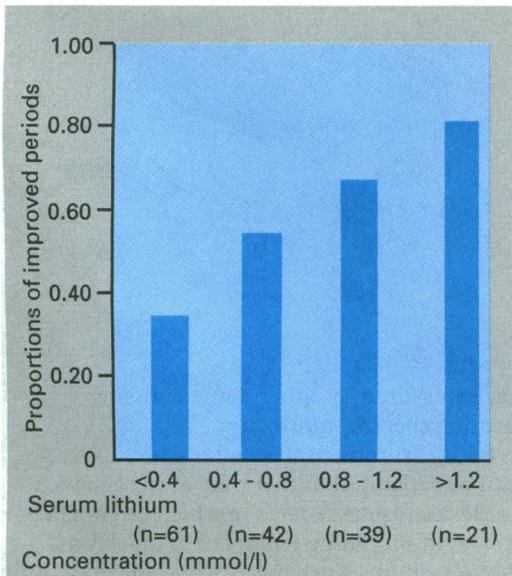
Even when a therapeutic effect has occurred it may be difficult to know whether the effect is optimal and whether it is attributable to the drug or to spontaneous remission. Furthermore, assessment of the extent to which lithium is contributing to a change in mood may be difficult in patients taking other mood altering drugs, as is commonly the case in the treatment of acute mania.

Furthermore, lithium is used for prophylaxis in patients with recurrent unipolar and bipolar affective illnesses. In such cases although a relapse may be evidence of a lack of therapeutic effect, you cannot be sure that the prophylactic dose is optimal in patients who remain in remission. In addition, such patients may well experience mild adverse effects of lithium, which occur commonly with therapeutic dosages. It may therefore be difficult to find a dosage that is effective and does not cause adverse effects.

Is there a good relation between the serum concentration and its therapeutic or toxic effects?

Because serum lithium concentrations vary quite widely between doses it is important that they are measured at a standard time. We will call this measurement the standard serum lithium concentration.

Interpretation of the results of studies of the relation between serum concentrations of lithium and its therapeutic effect has been made difficult by the fact that in many such studies measurement of serum lithium concentration has not been made at the same standard time after the previous dose. Despite this there is some evidence that a therapeutic effect is most likely to be achieved in patients with acute mania if the standard serum lithium concentration is above 0.8 mmol/l. There is also evidence



The higher the serum lithium concentration the greater the likelihood of a therapeutic response. In this case of acute mania the chance of a therapeutic response continued to improve up to relatively high serum concentrations.

The steady state standard serum lithium concentration in the treatment of acute mania is 0.8-1.2 mmol/l

The steady state serum concentration range for lithium in the prophylaxis of unipolar and bipolar affective illness is 0.4-0.8 mmol/l

Acute toxic effects

- Gastrointestinal symptoms—nausea, vomiting, diarrhoea
- Neuromuscular disorders—muscle weakness and fasciculation
- Central nervous system effects—confusion, ataxia, dysarthria, convulsions
- Cardiac arrhythmias
- Renal impairment

Long term adverse effects independent of serum lithium concentration

- Thirst and polyuria
- Tremor
- Weight gain (partly due to water retention, sometimes with oedema)
- Diarrhoea
- Hypothyroidism

that there is little benefit to be gained by increasing the concentration above 1.2 mmol/l and that the risk of adverse effects increases considerably above this concentration. Thus a reasonable therapeutic range for steady state standard serum lithium concentration in patients with acute mania is 0.8-1.2 mmol/l.

The evidence for a relation between the steady state standard concentration and a therapeutic effect in the prophylaxis of unipolar and bipolar affective illness is even less clear. The available evidence suggests that a lower range of concentrations is associated with a therapeutic effect compared with that for acute mania. It is common practice to maintain concentrations in the range 0.4-0.8 mmol/l, though there is little firm evidence to suggest that an optimal therapeutic effect will thus be obtained. It is likely, however, that by keeping the concentration below 0.8 mmol/l the risk of adverse effects will be reduced, though not eliminated.

Long term remissions can, however, occur in patients with serum lithium concentrations below 0.4 mmol/l and this is not seen as a reason for withdrawing treatment (in contrast to digoxin—see previous article). Conversely, in some patients a therapeutic effect in prophylaxis is achieved only by giving dosages associated with serum concentrations above 0.8 mmol/l.

It is generally agreed that the risk of lithium toxicity increases considerably when the steady state standard serum lithium concentration exceeds 1.4 mmol/l. The adverse effects that occur during acute toxicity are listed in the box. Note that lithium reduced renal impairment leads to worsened toxicity through retention of lithium.

In contrast it is not clear what the relation is between the steady state standard serum lithium concentration and the risk of adverse effects during long term treatment when the concentration is below 1.4 mmol/l. For example, it has been reported that only 10% of patients with serum concentrations within the range 0.4-1.3 mmol/l escape adverse effects. On the other hand, there is evidence that the frequency and severity of adverse effects may be reduced when serum concentrations are reduced from 0.9 mmol/l to 0.7 mmol/l. It should be noted, however, that this conclusion was based on retrospective comparisons of patients studied at different times.

The major long term adverse effects encountered by patients with serum concentrations in the therapeutic range are listed in the box. It is no longer thought that long term treatment with lithium is associated with renal damage. This is in contrast to the acute nephrotoxic effect that may occur when lithium concentrations exceed the therapeutic range.

Measurement techniques



Measuring the serum lithium concentration by flame emission photometry.

Lithium concentrations are measured by either flame emission photometry or atomic absorption spectrophotometry.

When collecting samples for measurement it is better to use clotted blood, from which serum can be separated, rather than anticoagulated blood. This is to avoid possible confusion in cases in which lithium heparin is used as an anticoagulant. Serum should be separated as quickly as possible and preferably within one hour, since there is movement of lithium into erythrocytes after that time.

Factors affecting the concentration

Factors that cause increased serum lithium concentrations

- Reduced glomerular filtration rate
- Sodium depletion
- Drugs:
 - Diuretics (principally thiazides)
 - Non-steroidal anti-inflammatory drugs (which may also reduce the glomerular filtration rate)
- Vomiting and diarrhoea
- Fever

As absorption of lithium from different oral formulations is variable different steady state serum concentrations may result if the formulation is changed.

Since lithium is eliminated from the body almost completely by renal excretion, factors that impair its excretion will cause increased serum concentrations. These factors are listed in the box.

Conversely, an increase in glomerular filtration rate, as occurs in the second half of pregnancy, will cause an increased rate of lithium excretion. (Note, however, that lithium is teratogenic and should not be given at least during the first trimester of pregnancy.)

Factors affecting interpretation

Drugs that may potentiate the toxic effects of lithium

- Neuroleptics:
 - Haloperidol
- Antidepressants:
 - Fluoxetine
 - Fluvoxamine
- Calcium antagonists:
 - Diltiazem
 - Verapamil
- Anticonvulsants:
 - Carbamazepine
 - Phenytoin

The actions of lithium may be enhanced by concurrent treatment with other drugs (see box) and by electroconvulsive therapy. It is not clear how to interpret the serum lithium concentrations in these circumstances. In general you should use the lowest dosages of neuroleptics possible if lithium is also to be used, and some psychiatrists withdraw lithium two or three days before electroconvulsive therapy.

Use of serum measurements

Case history: effects of sodium depletion

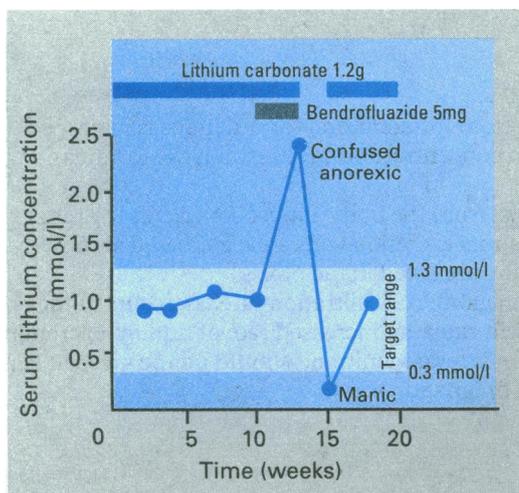
A 68 year old man developed a flu-like illness, with fever and diarrhoea. He continued to take lithium and within a few days became weak and drowsy, dysarthric, and ataxic. His serum lithium concentration was 3.1 mmol/l and he had acute renal failure. Lithium was withdrawn and he was rehydrated. Serial serum lithium concentration measurements over the next 24 hours showed that his serum lithium concentration was not falling quickly enough, and since he remained unwell he underwent dialysis, with a good result.

Conclusion

This case illustrates the need to warn patients to reduce the dosage of lithium and to seek medical advice if they develop fever or diarrhoea, or both. It also highlights the problems that can arise if there is impaired renal function.

It is possible to establish a dosage regimen of lithium in prophylaxis by giving 0.15-0.20 mmol/kg/day (that is, 10-14 mmol/day in a 70 kg patient, or about 400-600 mg/day of lithium carbonate) and measuring the serum lithium concentration no less than a week later, when a steady state can be assumed to have been reached. The dosage can then be adjusted in proportion to the desired target steady state concentration, as described below. The corresponding starting dosage in patients with acute mania would be 0.3-0.4 mmol/kg/day (about 25 mmol/day for a 70 kg patient, or about 1 g/day of lithium carbonate). The total dosage should be given in divided doses throughout the day.

It is possible to plan a dosage regimen in an individual patient more rationally by using the serum lithium concentration measured one or more times during initial treatment. The simplest method described entails giving a test dose of lithium carbonate (1.2 g) followed by measurement of the serum concentration 24 hours later. The serum concentration is then put into an equation that predicts the steady state serum concentration that would result from a daily maintenance dose of 1.8 g. As the maintenance dose is directly proportional to the steady state concentration this dose can be scaled down to achieve the target steady state concentration. For example, if a daily maintenance dosage of 1.8 g a day produced a steady state concentration of 1.2 mmol/l a dosage of 1.2 g would result in a concentration of about 0.8 mmol/l.



Thiazide diuretics increase the serum lithium concentration.

There is little merit in regularly checking serum lithium concentrations, and such checks may be reserved for times when you suspect that the patient's condition has changed in some way that would affect the concentration (for example, if a diuretic is given). Because of this it is important to warn the patient to seek advice when changes of this kind occur.

Case history: interaction with thiazide diuretics

A 58 year old woman had been well stabilised on lithium with serum lithium concentrations varying from 0.5 to 0.8 mmol/l. She developed peripheral oedema and was treated with bendrofluazide. She was admitted to hospital a week later with delirium. Her serum lithium concentration was 2.5 mmol/l. The lithium and diuretic were withdrawn and 36 hours later she was well. Lithium was restarted in the same dosage without subsequent problems. Her oedema was attributed to lithium and was treated satisfactorily with amiloride.

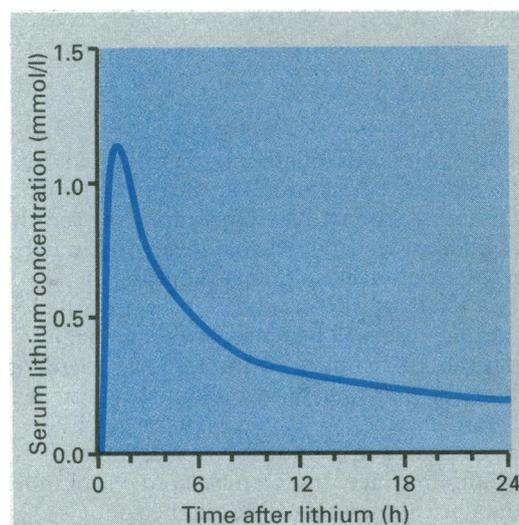
Conclusion

This case illustrates an interaction of lithium and a thiazide diuretic.

It may also be helpful to measure the serum lithium concentration when patients develop troublesome adverse effects, when the concentration may be used as a guide to reductions in dosage.

The serum lithium concentration may also be used to check patient compliance.

Timing of measurements



The serum sample for lithium measurement should be taken 12 hours after the last dose.

Two factors affect the timing of blood samples in patients taking lithium. Firstly, the considerable variation in the plasma lithium concentration during a single interval between dosages has led to the concept of a standardised time of sampling—namely, at 12 hours after the previous dose. Secondly, there is a diurnal variation in the handling of lithium by the body, and the half life of lithium is longer during the night than during the day. Although this has implications for the way in which a dose taken twice daily might be split, current regimens do not take diurnal variation into account.

It is therefore important when monitoring therapy to try to take the blood sample as close as possible to 12 hours after the last dose, and preferably always at the same time of day. This is possible in patients who are seen in the morning, having taken their last dose the previous night. It raises practical problems, however, in patients who are seen in the afternoon. These problems can be ameliorated to some extent if patients are given modified release formulations to take twice a day, since these formulations tend to even out the diurnal variations in serum concentrations.

The sources of the data shown in the graphs are Stokes *et al*, *Arch Gen Psychiatry* 1976;33:1080-4 for improved periods with serum lithium concentrations; Brodie, *Medicine International* 1988;59:2435-9 for the effect of bendrofluazide; and Amdisen, *Danish Med Bull* 1975;22:227 for lithium concentration *v* time, and are reproduced with permission of the journals.

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