

Follow-up of patients that use lithium

Lithium has been among the most important pharmacological treatments of psychiatric disease for more than 50 years. Its main indication is treatment and prophylaxis of bipolar disorder (manic-depressive illness). Lithium is also used to treat affective symptoms in schizophrenia and other psychological disorders. The therapeutic effect is well documented, but the drug can also interact with other drugs and cause serious side effects. The drug has a narrow therapeutic index and intoxications can occur at normal or low doses.

In 2006, about 7 700 individuals out of a population of 4.7 million in Norway used lithium (1). The drug's effect on bipolar disorder is well documented and new studies confirm that it reduces the frequency of attacks, suicides and attempts of suicide (2). Still, the use of new drugs with the same indication as lithium is increasing. Due to side effects with lithium, many patients are likely to change to a different drug with a less documented effect. Close follow-up of those who use lithium is needed to avoid side effects and therapeutic failure, and to ensure the best possible treatment.

The most important side effects with lithium are changes in renal function, thyroid function and parathyroid function. Other less serious side effects are diarrhoea, abdominal pain, rash, polyuria and hand tremor. Lithium intoxication is a potentially life-threatening condition (Box 1). Side effects are mainly related to the serum concentration and changes of this.

The mechanism of action is composite and only partly understood (3). Lithium affects a number of transmitter systems in the central nervous system; including serotonin and dopamine, both pre- and postsynaptic and intracellular via second messengers. Prolonged use will also regulate the activity of protein kinase C and other factors that affect the gene expression.

Lithium uptake is rapid and takes place in the upper part of the gastrointestinal tract. The maximum serum concentration occurs after two to three hours. Steady state concentration is achieved five to seven days after the start of dosing and after dose changes. Lithium is not bound to plasma proteins and is excreted unchanged in the kidneys.

Material and methods

This article is based on the authors' experience and literature retrieved through a Medline search with the terms «lithium» and

«adverse events», «side effects» and «pregnancy» in the period 1990–2007.

Practical accomplishment of treatment

To avoid side effects patients should be monitored closely at the start of treatment, during an increase of intensity and during maintenance treatment (tab 1).

The serum concentration should be measured regularly. The association between serum concentration and effect is well documented (4). The therapeutic index is narrow and there is a short distance between lack of effect and intoxication. In Norway, the reference range for the serum concentration is 0.5–1.0 mmol/L measured at steady state in serum and 12 hours after the last intake of lithium. A somewhat lower serum concentration is adequate for some patients when lithium is used in combination treatment of depression. At levels above 1.2 mmol/L, the risk of side effects will increase and levels above 1.5 mmol/L will have toxic effects in most patients. Levels above 2.0 mmol/L are considered to be serious- potentially lethal – poisonings. Serum concentrations should be measured frequently at the start of treatment- weekly the first month and thereafter monthly for half a year. Afterwards lithium should be measured every three to six months, depending on the patient's condition. For every dose change, the lithium level should be measured at steady state, after five to seven days.

The lithium level should be monitored closely in conditions that affect the fluid and electrolyte balance; e.g. diarrhoea, increased sweating and low fluid intake. Reuptake of lithium in the kidneys and thereby serum concentrations will increase with dehydration and hyponatremia. A high lithium level may lead to dehydration, because the drug blocks the effect of antidiuretic hormone on

the renal tubules. In serious cases the patient may risk intoxication with normal doses.

A number of drugs may affect the lithium concentration in serum when used concomitantly. ACE inhibitors will increase the serum concentration of lithium secondary to excretion of sodium. Thiazide diuretics will also lead to an increased concentration of lithium because of reduced renal excretion. The same applies to non-steroid anti-inflammatory drugs. With concomitant use of lithium and these drugs, the lithium concentration should be monitored closely, especially in periods when dosing is changed.

According to the manufacturer, lithium is contraindicated in the first trimester of pregnancy and should only be used on a strict indication in the second and third trimesters. Bipolar disorder during pregnancy is associated with a risk to both mother and child and in some situations pharmacological treatment is appropriate. Lithium in therapeutic concentrations gives a small but measurable increase in the prevalence of congenital abnormalities (5). Some congenital abnormalities in the heart have been observed, but these are very rare – and the risk must be balanced against serious psychological disease in the mother (6). Thyroid abnormalities in children whose mothers have taken lithium in pregnancy, have also been described. When lithium treatment is considered necessary, the lowest dose should be given, preferably as monotherapy. The kidneys' ability to excrete lithium may be affected during pregnancy and frequent serum monitoring is necessary.

Breast-feeding has been discouraged with lithium use. This is in contrast with more

Main message

- Lithium is a drug associated with serious side effects and risks of interaction and intoxication
- Patients should be examined thoroughly at the start of treatment
- Lithium users should be followed closely to prevent and diagnose side effects, intoxications and therapeutic failure
- Monitoring the serum concentration is important to avoid side effects, intoxications and therapeutic failure

recent studies (7,8) that show low levels and good tolerance of lithium in children who are breastfed. Lithium treatment should not be interrupted during breastfeeding, but the child should be closely observed with measurements of serum concentrations, renal function and the relationship between thyroid stimulating hormone (TSH) and thyroxine (T4); TSH/T4. Small children can easily become dehydrated with conditions such as diarrhoea and the common cold, thus endangering lithium intoxication. Children with such conditions should be followed especially close.

Side effects

Lithium may have serious side effects and physicians should be familiar with these. A systematic approach to prevent and reveal such side effects is appropriate. Such an approach is summarised in e-Table 2.

Reduced renal function

Lithium may harm the glomerular function. For the majority this damage will be small, and seriously reduced glomerular function and renal failure are rare side effects (9). Risk factors for such renal damage are long-term use of the drug, lithium intoxications, concurrent use of other drugs and underlying somatic disease. If the serum creatinine level is higher than 140 mmol/L, the patient should be referred to a specialist in kidney disease or internal medicine with special competence in kidney disease (7). For women and persons with a small muscle mass the value that will trigger an examination will be smaller.

Diabetes insipidus

Renal diabetes insipidus may affect about 10% of those who have used lithium for a long time (15 years or more) (10). The anti-diuretic hormone (ADH) blocks tubules of the kidneys and thereby leads to a decrease of urine concentration. This will lead to an increased volume of urine and dehydration after a while. For those treated with lithium this is especially unfortunate, as dehydration may lead to retention of the drug and lithium intoxication. Risk factors for intoxication are concurrent treatment with other drugs, other somatic disease and high age. If the patient develops progressive polyuria, the lithium dose should be reduced or other mood-stabilising drugs added. If this is not possible, lithium should be discontinued. If discontinuation is not possible because of treatment of the main disease, one may add treatment with the diuretics amiloride or chorthiazide, either together or separate (10). The serum concentration of lithium must be monitored closely because of the risk of interaction.

Hypothyroidism

15–30% of those treated with lithium develop hypothyroidism (11). Lithium inhibits both uptake of iodine in the thyroid and release of T4. It is therefore recommended to

measure TSH/T4 when treatment is started, then after 6 months and thereafter annually. Hypothyroidism should be treated with thyroxine. It is not recommended to discontinue treatment with lithium. Known risk factors for development of hypothyroidism during treatment with lithium are pre-existing positive antithyroid oxidase antibody (anti-TPO), positive family history, high level of TSH at start, increase of weight and high values of lithium. Women are somewhat more vulnerable than men. Presence of risk factors requires extra close monitoring of the patient, but is not a contraindication for lithium treatment (12). Some patients may also develop transient hyperthyroidism.

Hypercalcemia

Hypercalcemia is a relatively common side effect, with a reported prevalence of 6–50% (13). However, it is rare that the condition is so serious that it has clinical consequences. The calcium level is usually mildly elevated, and parathyroid hormone (PTH) within the normal range. The mechanism behind this may be that lithium has an antagonistic effect on the calcium receptors that control the excretion of PTH and thereby trigger PTH excretion at higher levels of calcium. With moderate hypercalcemia (S-calcium < 2.75 mmol/L) it is not necessary to discontinue the lithium treatment unless there are clinical manifestations of hypercalcemia. If calcium is substantially elevated (< 2.75 mmol/L) or clinical manifestations are present, one should consider exchanging to another mood-stabilising drug. If this is not possible parathyroidectomy should be considered (14).

Weight gain

11–65% of those who use lithium experience weight gain (15). The mean weight gain is 4–5 kg, but about 20% of patients will gain 10 kg or more (16). The cause of

Box 1

Signs of lithium intoxication

- Nausea
- Speech disturbance
- Increased shaking
- Tiredness / drowsiness
- Diarrhoea
- Ataxia
- Muscle weakness
- Nystagmus

the weight gain is not known. It has been suggested that lithium stimulates appetite through a direct effect on hypothalamus. Furthermore, polyuria is a side effect that leads to thirst. For many the choice will be sugar-containing drinks with a high amount of calories. Overweight at the start of treatment is a risk factor for weight gain. Concurrent treatment with other drugs increases the probability for a patient to gain weight. Women are more susceptible than men. The patients should be monitored closely – with weighing at the start of treatment and every month thereafter. With an increase of weight of more than 1 kg one should intervene with diet suggestions and exercise. It may be appropriate to switch to another drug, but several of the alternatives, including anti-epileptics and antipsychotics, may also lead to weight gain. This underlines the importance of prevention by giving advice on diet and exercise before start of treatment.

Conclusion

Lithium still has a central place in treatment and prevention of bipolar disorder. Close monitoring and medical follow-up may

Table 1 Laboratory tests

Test	Start of treatment	During the initial treatment phase	During the maintenance phase
Lithium level in serum		Every week for a month Every month the first 6 months At every dose change the lithium level is measured after 7 days	Every 3–6 months At every dose change
TSH/T4	All	After 6 months	Every 6 months
Anti-TPO	All		
Calcium	All	After 6 months	Annually
S-Creatinine	All	After 6 months	Every 6 months
Electrolytes	All	After 6 months	Annually
Pregnancy test	Women		
ECG	More than 40 years of age or known risk factors for cardiac disease		

prevent serious side effects, interactions and intoxications.

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